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ERRATUM

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PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

TWENTY-FIFTH ANNUAL GENERAL MEETING

THE TWENTY-FIFTH ANNUAL GENERAL MEETING was held in Sheffield on Friday and Saturday, May 22 and 23, 1931, in the Mappin Hall, Applied Science Department of the University. The Attendance Book for the Meeting was signed by 130 members. The proceedings began at 10 a.m.

The President, Sir William Hale-White, was in the Chair.

The Minutes of the last Annual Meeting having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

Election of Officers

President. Professor A. J. Hall was elected President for 1931-32. On his election he took the Chair and expressed the thanks of the Association to the retiring President for his services during the past year.

Election of Officers, members of the Executive Committee, Extra-ordinary members, and Ordinary members followed.

President. Professor A. J. Hall.

Treasurer. Dr. H. Morley Fletcher.

Secretary. Dr. H. Letheby Tidy.

Members for England :

Professor T. Beattie.
Dr. W. Langdon Brown.
Dr. J. G. Emanuel.
Dr. Gordon M. Holmes.
Dr. A. E. Naish.
Dr. R. A. Young.

Members for Scotland :

Dr. A. Greig Anderson.
Dr. J. Eason.
Dr. Ivy Mackenzie.

Members for Ireland :

Sir Thomas Houston.
Dr. R. J. Rowlette.
Professor V. M. Synge.

As Extra-ordinary Members :

Sir Ashley W. Mackintosh, M.D.
Dr. Harry Campbell.
Dr. R. A. Fleming.
Dr. W. Hunter, C.B.
Dr. A. F. Voelcker.

Ordinary members :

George Ernest Beaumont, M.D., Physician, Middlesex Hospital.

Edward A. Carmichael, M.B., Assistant Physician, National Hospital for Nervous Diseases, Queen Square.

ASSOCIATION OF PHYSICIANS

William Tregonwell Collier, M.D., Assistant Physician, Radcliffe Infirmary, Oxford.
Maurice Davidson, M.D., Physician, Brompton Hospital for Consumption.
Arthur Cecil Hampson, M.D., Assistant Physician, Guy's Hospital.
Charles F. Harris, M.D., Physician, Children's Department, St. Bartholomew's Hospital.
Thomas Cecil Hunt, M.D., Assistant Physician, St. Mary's Hospital.
James Maxwell, M.D., Chief Assistant, Medical Unit, St. Bartholomew's Hospital.
Robert Henry Micks, M.D., Physician, Sir Patrick Dun's Hospital, Dublin.
Arthur Arnold Osman, M.R.C.S., Clinical Research Fellow, Guy's Hospital.
James K. Slater, M.B., Assistant Physician, Royal Infirmary, Edinburgh.
David Smith, M.D., Senior Assistant Physician, Royal Infirmary, Glasgow.

Presentation of Treasurer's Accounts. Dr. Morley Fletcher (Treasurer) presented the Annual Accounts which were adopted. They showed a balance of £301 12s. 9d.

Selection of Place of Meeting for 1932. A letter was read from Professor Moorhead inviting the Association to meet in Dublin. The invitation was cordially accepted.

Before proceeding to Scientific Business, the President referred to the deaths of Sir Byrom Bramwell and Professor Glynn.

SCIENTIFIC BUSINESS

Friday Morning

1. DR. E. F. SKINNER on *Examination of the Cerebrospinal Fluid with Ultra-violet Light*. The passage of ultra-violet light waves was suggested as a possible method of revealing variations in the cerebrospinal fluid, and a series of examinations have been made, using tungsten and copper as a source of ultra-violet waves. The alterations in the normal spectrum which occur in certain diseases were discussed, the most marked being in tuberculous meningitis.

2. DR. E. MELLANBY discussed *The Experimental Production and Prevention of Spinal-cord Degeneration*. Degeneration of groups of fibres in the spinal cord of puppies, demonstrable by Marchi's and Weigert's methods, can be experimentally produced by feeding them on mixed diets which are rich in cereals and deficient in vitamin A. If ergot of rye be added to the same diets the degenerative processes are more intensely produced. To a less degree the addition of the germ of cereals, e.g. of wheat and rye, also increases the degenerative changes. In all cases, even when ergot is added to the food, the animals remain in good health and develop no demyelination of the cord fibres if foodstuffs containing vitamin A are eaten. Both vitamin A and carotene also bring about great improvement in the condition after it has developed. Thus it appears from this experimental work that this type of cord degeneration depends (1) on a neurotoxic action associated with ergot and possibly with cereals generally, and (2) the absence of a protective mechanism in which vitamin A and carotene play an important role. This work would appear to have a direct bearing on the aetiology and treatment of (a) convulsive ergotism in man, (b) the central nerve lesions of pellagra, and (c) lathyrism. The possibility that vitamin A played a part in subacute combined degeneration of the cord in pernicious anaemia was also alluded to. The protective action of foods rich in vitamin A and carotene against the neurotoxic agents described was so great that it seemed advisable to test these foods as therapeutic agents in all cases of spinal-cord degeneration, including general paralysis, tabes dorsalis, and disseminated sclerosis.

Dr. Yates referred to two cases of dementia paralytica which had been placed on a diet rich in vitamin A and carotene, as suggested by Dr. Mellanby, and had greatly improved.

Drs. Parkes Weber, D. Campbell, and McNee discussed this communication.

OF GREAT BRITAIN AND IRELAND

3. DR. C. L. SUTHERLAND (introduced) gave a communication on *The Clinical Aspects of Silicosis*. Silicosis occurs in this country in workmen usually over 35 years of age, but cases may occur under that age. It may occur in young adults in the form known as acute silicosis. The condition may be latent and only appear some years after the worker has left his occupation. The length of exposure to the dust is usually from 15 to 20 years, but this depends on intensity of the exposure. The diagnosis rests on the radiological examination, the X-ray film showing a mottling of the lung substance. Symptoms may not be present at the early stage and the physical signs detected are limitation of movement, a flat note on percussion and diminution of breath sounds. As the disease progresses, the symptoms and physical signs become more pronounced. On the X-ray film the nodules tend to coalesce and later to form masses. The presence of tuberculosis in silicosis cases is detected by the sputum examination, by the physical signs, and, in the X-ray film of asymmetrical shadowing, or in some cases, denser shadows at both apices.

4. PROFESSOR M. J. STEWART (introduced) on *Observations and Experiments on Pulmonary Asbestosis*. He described the morbid anatomy from his experience of 9 cases seen at autopsy, emphasizing the diffuse character of the pulmonary fibrosis as compared with the nodular lesion in silicosis. In the later stages bronchiectasis appears, but it is exceptional for tuberculosis to be superimposed. The 'asbestosis bodies' which are formed in the lungs as a result of interaction between the asbestos fibre and the body fluids were described and their nature discussed. Exposure of guinea-pigs to ordinary factory concentrations of dust for periods ranging from 3 to 14 months has led constantly to the appearance of bodies in the lungs.

With regard to these two communications (3 and 4), Dr. L. G. Irvine (introduced) referred to occurrences of silicosis in gold mining in South Africa. Formerly there were over 800 cases a year, but this had been reduced to less than 300. Silicosis and tuberculosis are independent affections, but each modifies the other when both are present.

Drs. R. A. Young, Wilkinson, and G. Murray, joined in the discussion which followed.

5. DR. GORDON M. HOLMES on *Vascular Tumours of the Forebrain*. This communication was based on five vascular tumours of the forebrain of the cavernous haemangioma type observed during the past two years. Such tumours constitute from 2 to 3 per cent. of all intracranial growths, and as they are of long duration and present only isolated symptoms, their diagnosis is often difficult. Epileptic phenomena are frequent, and symptoms of increased intracranial pressure appear late. The chief points in their differential diagnosis are the presence of naevi on the face, or of distended vessels in the neck and scalp, tortuosity of the retinal veins and the presence of a murmur in the head heard by the patient and usually audible on direct auscultation of the skull. In the five cases described, the tumours occupied the temporo-occipital lobes of the brain and visual symptoms were therefore present.

6. DR. H. CARLILL exhibited a man whom he stated to be suffering from *Hysterical Sleeping Attacks*.

2 p.m. to 3 p.m.

Demonstration of Clinical Cases, Pathological Specimens, and Radiographs and Specimens illustrating Silicosis at the Royal Hospital.

3 p.m. Afternoon Session

1. DR. F. PARKES WEBER discussed two cases (1) *Aplastic Anaemia treated with Blood Transfusion*, and (2) *Generalized Lymphosarcoma*. The first case was that of a young man with aplastic anaemia, whose life can be maintained only by repeated blood transfusions. The second case related to that of an elderly woman who died with extraordinarily rapid generalization of a lymphosarcoma-like growth, soon after the removal of a swelling under the lower jaw by radium treatment.

These cases were discussed by Drs. Poulton, Hurst, Stanley Davidson, and Tidy.

2. DR. O. LEYTON gave a communication on *Hyperglycaemic Glycosuria Anosos*. A number of patients under observation, whose sugar tolerance tests prove that they have had hyperglycaemic glycosuria, have eaten unrestrictedly without the administration of insulin, and nevertheless have not lost any power of storing carbohydrate as demonstrated by the sugar tolerance tests. Several of these patients have been subjected to tolerance tests after a week of diet with a low carbohydrate content, and again after a week of diet rich in carbohydrate. The typical difference which occurs in the diabetic subject has been absent. During the last five years he had seen several cases in which

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the renal thresholds for dextrose have been not less than 0.19 per cent. with histories of glycosuria for periods up to 20 years, during which time restricted diets have been the exception rather than the rule, and these when submitted to the tests mentioned above failed to show anything more than hyperglycaemic glycosuria. None of these patients had any symptoms of disease.

3. PROFESSOR A. RAMSBOTTOM reported a case of *Spontaneous Hyperinsulinism*, and discussed the possible causation. The patient was a children's nurse aged 44, who in 1923 unexpectedly became sulky and self-assertive. In 1925 she took a situation where she lived largely on tinned foods and seldom had any sweets. After a few months she complained of attacks of 'shakiness' and 'faintness', but did not actually faint. Subsequently she had attacks of loss of consciousness, petit mal, and hysteria. In 1930 she was admitted into the Bradford Royal Infirmary under Dr. Eurich, and while there had attacks of loss of consciousness every day about 5 a.m. In these attacks she became very pale, sweated profusely, and had a very weak pulse. Hypoglycaemia was suspected, and an estimation of the blood-sugar gave 0.046 per cent. Glucose ($\frac{1}{2}$ lb. daily) was administered. The blood-sugar rose to a maximum of 0.064 per cent. with an appreciable improvement in the patient's condition. On February 24, 1931, she was admitted into the Manchester Royal Infirmary. The blood-pressure was 115/75, and the blood-sugar 0.046 per cent. Five days later she became stuporose. The blood-sugar was now 0.031 per cent. and fell to 0.028 in three days. She remained in coma for five days. Adrenalin (1 in 1000) was administered subcutaneously. Her mental condition improved somewhat. The effect of the administration of adrenalin on the blood-sugar was as follows:

Blood-sugar	5 minutes after giving adrenalin	= 0.041 per cent.
" "	15 " " " "	= 0.049 " "
" "	30 " " " "	= 0.060 " "
" "	1 hour " " " "	= 0.071 " "
" "	2 " " " "	= 0.081 " "
" "	2½ " " " "	= 0.073 " "
" "	3 " " " "	= 0.065 " "

As the coma increased on the following day, 400 c.c. of a 20 per cent. solution of glucose were given intravenously, and the coma rapidly became less profound. Subsequently 1 lb. of glucose was given daily by the mouth. The condition improved and consciousness returned, but later epileptiform convulsions and hysterical fits occurred. A laparotomy was performed but the pancreas appeared normal. She is still having 1 lb. of glucose daily, but in spite of this has frequent hysterical outbursts at night, and on the whole there is little perceptible improvement in her mental condition. The actual cause of the hypoglycaemia in this case has not been determined. Possibly the islet tissue of the pancreas is increased. There is no evidence of a cerebral lesion.

Sir Humphry Rolleston suggested that the condition was due to liver deficiency.

Dr. Brain described similar cases.

Drs. Morris, Parkes Weber, and F. R. Fergusson joined in the discussion.

4. DR. H. F. MOORE on *A Clinical Study of Achlorhydria*. Fractional test-meal examination was done on 1,171 patients between January 1, 1927 and March 31, 1931; of these 256, or 21.8 per cent. had complete achlorhydria. Forty-four cases of secondary anaemia of doubtful aetiology were studied, and of these 30, or 68.1 per cent. had achlorhydria. Seventy-nine cases of diabetes mellitus were examined, and 33 of them, or 41 per cent. had achlorhydria. Forty cases of hyperthyroidism were examined, and 32, or 80 per cent. had achlorhydria. In the entire series there were 97 gastro-intestinal and 68 miscellaneous cases with achlorhydria. Two patients with diabetes mellitus, one with osteogenesis imperfecta and one with hyperthyroidism, all of whom had achlorhydria, developed the particular form of anaemia so often associated with achlorhydria. Precautions were taken to ensure that there was true achlorhydria wherever doubt existed, e.g. by washing out the stomach before the test meal or by the hypodermic injection of histamin. The following facts were observed before treatment in the 30 cases of secondary anaemia associated with achlorhydria:—Twenty-six of the cases were females and four were males, seventeen had atrophic glossitis; the average erythrocyte count was 3,600,000 and the average leucocyte count was 4,870 per cm.; the average haemoglobin content was 50 per cent., the lowest being 15 per cent. The blood bilirubin was normal in all, and in only two was the spleen palpable (one of these was a case of the Plummer Vinson syndrome). The anaemia was non-megalocytic in type. Twenty-one cases submitted themselves for a sufficient length of time to treatment by oral iron therapy with excellent results, both symptomatically and as judged

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by the blood-count. It was found that iron in the ferrous form (10 gr. per day) gave better results than in the ferric form (60 gr. per day). Hydrochloric acid in the treatment by mouth seemed to be of value only in relieving the associated gastro-intestinal symptoms. Test-meal examination of twelve successfully treated cases failed to show hydrochloric acid after the blood had been restored to normal. Liver extract for pernicious anaemia was valueless in treatment. The significance of achlorhydria and its role in producing secondary anaemia was discussed.

Dr. Hurst stated that in many cases of achlorhydria, if the stomach is washed with hydrogen peroxide, hydrochloric acid returns.

Professor Ellis also spoke.

5. DRS. ALEXANDER GOODALL and J. K. SLATER (introduced) gave a communication on *The Treatment of Cases of Disseminated Sclerosis with Liver*. Twelve cases had been long enough under treatment to show results. One, a case of ten years' duration, had regained bladder control and the speech and gait had improved within a month. Six cases unable to stand without support, became able to walk briskly. Four cases previously unfit because of weakness, tremor, bladder trouble, or mental silliness, had all returned to work, and one had made a complete recovery. The suggestion was offered that disseminated sclerosis might be a deficiency disease. The treatment employed had been the ingestion of $\frac{1}{2}$ lb. daily of lightly cooked liver. No observations with liver extracts had been made.

Dr. Gordon Holmes expressed the opinion that there was no substantial evidence at present that disseminated sclerosis is a deficiency disease.

6. PROFESSOR STANLEY DAVIDSON described *Three Cases of Macrocytic Haemolytic Anaemia*. All three cases occurred in middle-aged women whose symptoms were those of severe anaemia. The essential haematological features were as follows:—Severe oligocythaemia in two cases, the red cell count being 1,000,000 or less. Colour index over unity, varying from 1.1 to 1.5. The presence of both megaloblasts and normoblasts in the peripheral blood. The presence of marked megalocytosis as demonstrated by the Price-Jones graphical method. Normal gastric secretion. No abnormal fragility. High icterus indices, with a positive indirect van den Bergh reaction, denoting haemolytic anaemia. Waves of haemolysis recognized by a falling blood-count and increasing icterus index followed by waves of intense bone-marrow reaction, recognized by reticulocyte counts of from 25 to 50 per cent. In two of the cases massive enlargement of the spleen was present. In no case was there any enlargement of the lymphatic glands.

The relations of the group to pernicious anaemia and acholuric jaundice were discussed.

The *Annual Dinner* was held at the Victoria Hotel at 8 p.m. The President, Professor A. J. Hall, was in the Chair. The official guests included the Vice-Chancellor of the University, the Master Cutler, the Lord Mayor, the Dean of the Faculty of Medicine, the Chairman of the Royal Hospital, and the Chairman of the Royal Infirmary. 136 members and guests were present.

Saturday Morning

1. DR. C. H. MILLER discussed *The Relation of the Gall-bladder to Cardiac Pain*. Cases were referred to in which the diagnosis of cardiac pain had been made and the symptoms had been relieved after the passage of gall-stones. Personal experiences of relief of cardiac pain after cholecystectomy were given. In a series of 200 cases of gall-bladder disease, it was found that severe coronary atheroma, myocardial fibrosis and recent cardiac infarction, together, were $3\frac{1}{2}$ times as frequent as in a series of cases in which the gall-bladder was healthy. The removal of a diseased gall-bladder in cases of cardiac pain was advocated for two reasons: (1) the probability that pain would be relieved; (2) the risk was not great.

Drs. Goodall, Hurst, and other members agreed with Dr. Miller.

Dr. Hamil referred to the association of appendicitis with cholecystitis.

2. DR. A. F. HURST on *Megacolon and Eventration of the Diaphragm*. Megacolon is more common in adults than in children, although the condition has hitherto been rarely recognized except in children (so-called Hirschsprung's disease). He had seen

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25 cases: 7 boys, 1 girl, 9 men, 8 women. The condition is always acquired; it is the result of achalasia of the anal sphincter caused by degeneration of Auerbach's plexus, owing to which the sphincter remains closed instead of relaxing in the act of defaecation. The resulting obstruction leads to overaction of the pelvic colon and rectum, the muscular coats of which become hypertrophied. In spite of this, evacuation of faeces and gas is incomplete. Owing to the thick muscle of the rectum and the absence of a mesentery only a slight degree of dilatation occurs, but the thinner walled and movable pelvic colon becomes enormously enlarged, both in diameter and length; the dilatation rarely extends beyond the junction of the pelvic colon with the iliac colon, as the latter is also devoid of a mesentery. The pelvic colon generally reaches the left dome of the diaphragm and may extend above the liver under the right dome. A secondary kink may occur at the pelvi-rectal junction, but the primary obstruction is always at the anal sphincter. Megaecolon does not necessarily give rise to any symptoms, though constipation is generally present; toxæmia never occurs unless aperients are taken, but attacks of colic caused by over-distension with gas are common. Treatment by dilatation of the anal sphincter always gives more or less complete relief, and operative treatment is never indicated.

Drs. Starling, and Parkes Weber discussed this communication.

3. DR. HARRY CAMPBELL, in a contribution entitled *Some Aspects of British Diet*, gave an interesting account of the influence of agriculture, and of the effect on the teeth of modern diet.

4. DR. T. WARDROP GRIFFITH gave a communication on *Division of the Left Auricle into Two Compartments*. He showed a specimen of a heart from a child of six months old, who died with signs of congestive heart failure. The left auricle was divided into two chambers by a membranous septum; the upper chamber received the pulmonary veins; the lower chamber communicated with the left ventricle through a normal mitral valve aperture and with the cavity of the auricular appendix. A probe passed through a slightly patent foramen ovale showed that the right auricle was in communication with the lower of the two chambers of the left auricle. An imperfect fringe of vegetations was found on the margin of the aperture of communication between the upper and lower chambers, and this aperture was large enough to admit of the passage of a goose quill. He was inclined to regard the dividing septum as an exaggeration of, and allied to, the more imperfect septa or bands which are found in some cases to spread from the valvula foraminis ovalis ('retinacula'). In showing his first case of 'fibromuscular band passing across the left auricle' in 1896, Dr. Griffith had suggested to the Anatomical Society the possibility of the condition being due to an imperfect opening out of the communication between the left half of the primitive auricle and the left, or pulmonary sinus venosus, and this is supported by the present specimen.

5. DRS. F. R. FRASER, C. F. HARRIS, and J. A. DAUPHINEE (introduced), on *Calcium and Phosphorus Metabolism in Hyperparathyroidism*. Three cases of hyperparathyroidism were investigated, and the calcium and phosphorus metabolism estimated before and after removal of parathyroid tumours. The conclusions were:

(1) That the condition of hyperparathyroidism may at times diminish greatly in activity.

(2) That the phosphorus metabolism does not follow the calcium metabolism as might be expected.

(3) That phosphorus may be stored while calcium is being excreted in quantities in excess of the intake.

(4) That the most probable explanation is that phosphorus under these conditions is stored in the body in some form other than the calcium phosphates of bone.

Dr. Findlay did not believe that tetany is necessarily connected with the parathyroid.

Drs. D. Hunter and Ritchie discussed several points.

6. DR. C. G. IMRIE discussed *Some Observations on Post-encephalitic Bradypnoea*. A male, aged 31 years, had epidemic encephalitis in March 1924. He came under observation in September 1928, presenting clinical features of post-encephalitis parkinsonism and bradypnoea. The respiratory rate at complete rest varies from three to six per minute, the tidal air from 1,000 to 2,000 c.c. The diaphragm, examined roentgenologically, moves normally with inspiration, but the return to the expiratory position is very slow. The respiratory rate could be controlled volitionally; it quickened during work, speech, and to a slight degree in sleep. It was suggested that the condition was

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due to the persistence of inspiratory tonus, inhibition was not initiated until the lung tissue was distended to a greater degree than normal, and then the inhibition was incomplete giving rise to the prolongation of expiration.

The President stated that this is the only recorded case of bradypnoea following epidemic encephalitis.

7. DR. IAN G. W. HILL (introduced), under the title of *Carotovagal Reflexes*, gave an account of the reflexes arising from the carotid sinus and controlling heart-rate, blood-pressure, and respiration. The results of animal experiments were detailed, together with observations made upon the human subject during operations on the region of the carotid bifurcation, and the views of Hering regarding the reflex origin of bradycardia and 'vagal pressure' in man were substantiated.

2 p.m. to 3 p.m.

Demonstrations of Clinical Cases, Pathological Specimens, and Radiographs and Specimens illustrating Silicosis at the Royal Hospital.

3 p.m. Afternoon Session

1. DR. ROBERT COOPE gave a note on *Unresolved Pneumonia and Early Bronchiectasis*. He believed that both in children and adults, the important aetiological factor was a broncho-pneumonia which caused damage to the bronchioles, and invasion of the peribronchial, alveolar, and interstitial tissues. A broncho-pneumonia might result in complete recovery; in merely peribronchial thickening; an interstitial scarring which might extend also to the pleura; or in damage so severe as to bring about fibrotic dilatation of weakened bronchi, i.e. actual bronchiectasis.

2. DR. L. FINDLAY recorded the result of an *Analysis of 688 Examples of the Rheumatic Infection (Arthritis, Chorea, and Carditis) occurring during Childhood*. The conditions had occurred between the years 1911 and 1929, and the whole material was reviewed in 1930. With the exception of six of the examples, the ultimate fate or the present condition, if still alive, was known of them all. About 30 per cent. of the children had escaped implication of the heart. Of the cases in whom the heart was affected, one half, i.e. 30 per cent. of the total number died within ten years of the onset of the infection: a very large proportion, 37 per cent., died during the first year of the disease. The remaining 30 per cent. are still living, but more or less incapacitated. The ultimate fate of this group is problematical, but because the majority of rheumatic cardiac deaths occur during the age period, 35 to 45 years, it is presumed that for the most part they will die on reaching this age period of life. Since the age incidence of arteriosclerosis synchronizes in its onset with the period of increased rheumatic cardiac deaths, it is suggested that it is the onset of the degenerative cardiovascular changes which decides the fate of those examples of rheumatic heart disease who reach adult life.

3. DR. D. MCALPINE made *Some Observations on Essential Arterial Hypertension*. He described several cases, three of them being in men under the age of 31, in which there was retinitis with papillitis associated with raised blood-pressure and little evidence of renal damage. The ophthalmoscopic picture was that described as 'renal' or 'albuminuric' retinitis. The term 'hypertensive' retinitis had recently been introduced in America to describe the retinal changes associated with essential hypertension, and his cases would seem to fall into this category. Manometric readings of the cerebrospinal fluid showed that as a rule the rise in intracranial tension was slight and was seldom great enough to account for the papilloedema. The aetiology of the retinitis in hypertension was discussed, and some evidence was brought forward in support of the theory of arteriole spasm.

4. DR. TERENCE EAST discussed *Calcification of Aortic Valves*. The calcification was most pronounced in the depth of the cusps. Usually there was fusion of the cusps. Sometimes calcified masses spread down into the septum, and in two instances had caused disturbances in conduction. There might also be calcification of the mitral valve, and in some cases the mitral valve alone was affected. The cause was obscure. Rheumatism is unlikely in view of the incidence on the aortic valves. Syphilis is not found. Certain points suggest an inflammatory cause—a very subacute endocarditis—but infarcts do not occur. Possibly the degenerative process causes the condition in some instances, and sclerosing endocarditis in others. Aortic stenosis, without a mitral lesion, is almost invariably due to this disease when it is met with in middle age or later.

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QUANTITATIVE OBSERVATIONS ON PROTEINURIA IN NEPHRITIS¹

By PHYLLIS M. TOOKEY KERRIDGE

(From the Medical Unit, The London Hospital)

THE literature which has appeared in the last hundred years on the proteins which are found in the urine in nephritis is very large, but fortunately there are two recent German monographs which give it extensive surveys (1, 2). The custom seems to have been, whenever quantitative work has been done on the subject, to measure and to consider the concentration of protein in the urine rather than the total amount of protein excreted. The purpose of the present paper is to suggest that this custom is unwise for this reason: the protein concentration has been found to vary inversely as the volume of urine that is passed. Moreover the total protein excreted per day has been found to be more characteristic of the patient's condition, and the stage of his disease.

No attempt has been made to distinguish between the different types of nephritis and nephrosis, as it appeared to be unnecessary for the present purpose; the term 'nephritis' is used in this paper to include both nephritis and nephrosis. The patients on whom these observations were made were in different stages of various types of the disease. The total number of patients studied in this series was twenty-three, and in fifteen of these the investigations were continued over many weeks.

The protein estimations were made by difference between the total and non-protein nitrogen in the urine, as determined by the micro-Kjeldahl method in the earlier part of the work. Latterly the protein determinations were done by a simpler method, an account of which has been already published elsewhere (3).

The Daily Variation in Protein Concentration

Figure 1 shows the daily variation of the protein concentration for a typical eight-day period in the case of a patient, C. R., of whom records were kept of every specimen of urine passed every day for four months. It will be easily seen that the protein concentrations were very much higher in the evening and early morning specimens than in the others, and that an increase in the protein concentration of moderate degree occurred in the

¹ Received June 3, 1931.

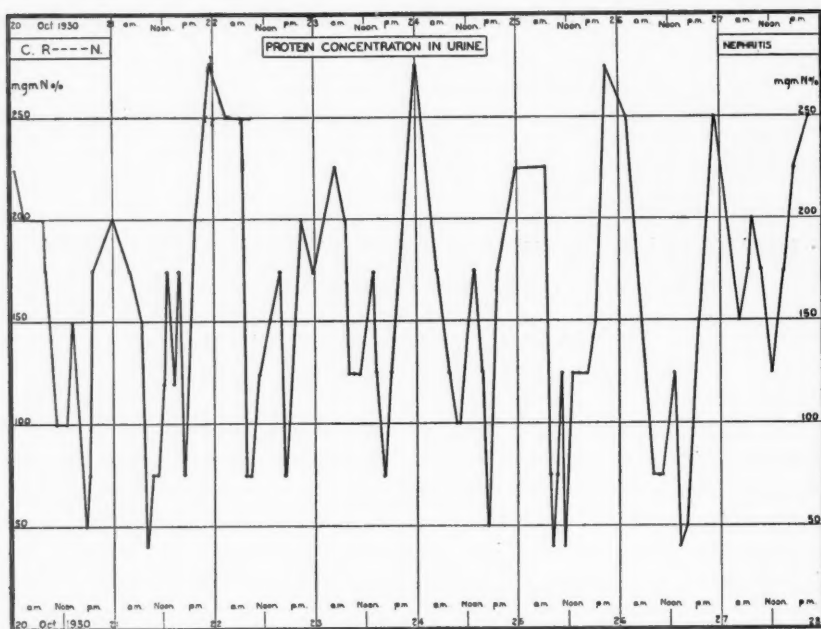


FIG. 1.

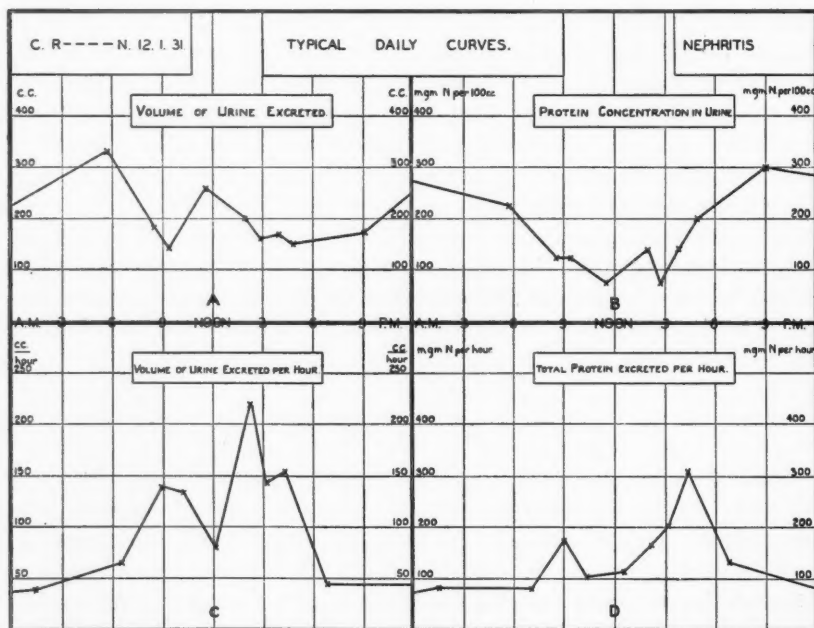


FIG. 2.

middle of each day. These variations are very striking in a case like this, when the total protein loss is high, but they occur similarly in other patients when the amount is less, although the differences are then not so noticeable. The concentration of protein in the urine of a nephritic patient is highest in the evening and early morning; it is lowest and very variable during the day. The reverse is true of orthostatic albuminuria. Although these observations were made from quantitative estimations of fair accuracy, the diurnal variation is so gross in a case such as that shown in Fig. 1 that the observations could have been made by any ordinary qualitative test, such as the acetic acid boiling test. The difference between the day and night specimens, for instance, may be of the order of 'a cloud' to a half volume.

Fig. 2 illustrates further considerations of a typical day of the same patient. Chart 2A shows the volumes of urine and the times at which they were passed. Chart 2B shows the protein concentrations in the respective specimens, and is analogous to a part of Fig. 1, but is drawn on a different scale. It shows again the high evening and early morning values, and the moderate rise during the day. The volume of urine excreted per hour has been calculated and plotted in chart 2C. It will be seen that the amount is much greater by day than by night, as would be expected. The total amount of protein lost per hour is shown in chart 2D. It will be noticed that the total amount of protein excreted was greater by day than by night. Thus more protein is lost by day than by night, although it is passed at a lower concentration. This is accounted for by the greater relative increase in the volume of urine excreted during the day.

The Effect of Getting Up

Fig. 3 is taken from data on another patient, J. W. He had improved considerably clinically, but he still had a fair amount of protein in his urine. As he seemed to have reached a stationary stage, he was being sent to a convalescent home, and was therefore allowed to be up in the wards for a few hours each day before leaving hospital. Immediately the daily volume of urine decreased and the protein concentration increased; in four days the former was halved, the latter doubled. Calculation showed that the total daily protein loss was no greater than before. It seems probable that the decrease of urine volume was in large part or wholly due to the physiological effects of change of posture, increase of perspiration, &c., and that the change of protein concentration was secondary thereto, and that neither were of such serious import as they at first appeared.

The Effect of Diuretics

Figs. 4 and 5 illustrate the importance of considering total protein loss, when judging the effects of diuretics in nephritis. Fig. 4 shows the changes which followed the administration of urea to the patient, J. W. His weight fell suddenly; the daily volume of urine was nearly trebled; and the protein concentration was considerably reduced. But the total protein lost per day

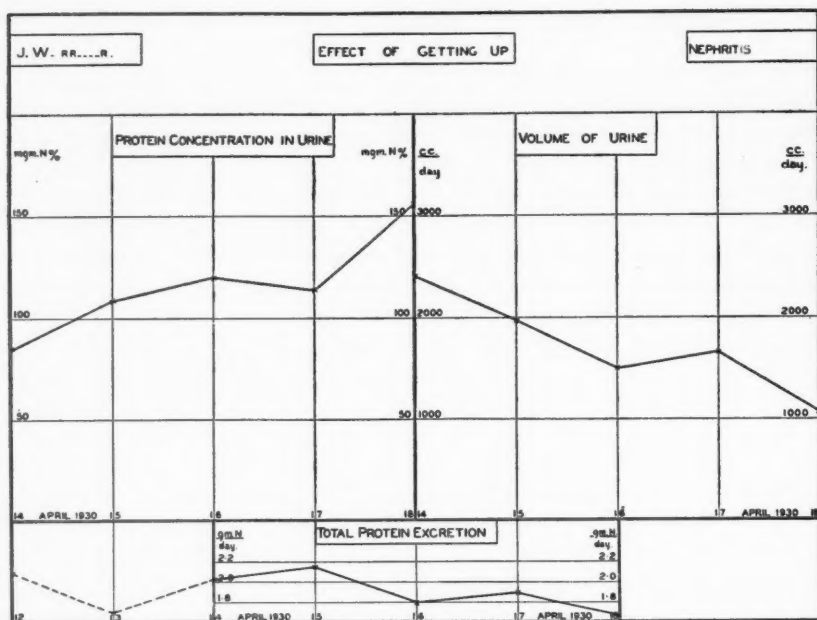


FIG. 3.

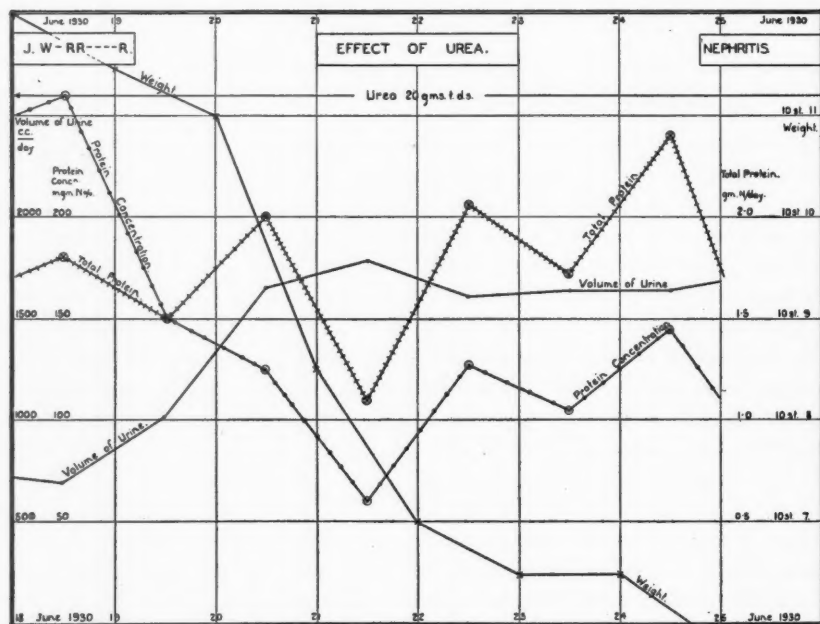


FIG. 4.

continued within its former limits; as it also did later, when in spite of the continuance of the urea administration, the weight again rose, the volume of urine decreased, and the protein concentration rose.

Fig. 5 shows the records for six weeks of another patient, M. B., during which time she was given varying large doses of potassium citrate. It will be seen that the protein concentration in the urine decreased after the first administration, and again on subsequent increases of the dose, but that these reductions were not maintained. The total protein in the urine varied between the same limits throughout almost the whole period, but it did fall temporarily after the initial administration of potassium citrate at the same time as the fall in protein concentration, there being no corresponding increase in urine volume at that time.

The Effect of Infection

Fig. 6 represents some data obtained immediately before and during the infection which ended the life of the patient, C. R., who was under observation for ten months. One day he had a sudden attack of abdominal pain. Dull pains in his abdomen and trunk continued during the next few days, his temperature rose, and his oedema increased considerably. Seven days later he had an attack of dyspnoea and cyanosis. His chest was aspirated and $1\frac{1}{2}$ pints of clear fluid withdrawn. It was necessary to aspirate his chest again on the following day, when a thin pus was collected, which culture showed to contain haemolytic streptococci. He died two days later. With the onset of the infection, the daily volume of urine fell and the average protein concentration, which was already high, rose to double its former value. The figures obtained on one night were the highest ever recorded in this series. Yet the daily total protein loss did not differ from its previous amount, thus showing that it was unaffected by the infection with the haemolytic streptococcus.

Discussion

It is not proposed to discuss at the present time the significance of the above observations with regard to theories as to the source of the protein found in the urine in nephritis. The aim of the paper is to illustrate, by examples, the practical point that misconceptions may arise from the customary consideration of the concentration of protein in the urine only. Since the protein concentration tends to vary inversely as the urine volume, it is obvious that the total protein loss per twenty-four hours gives more valuable information than the concentration in any single specimen. However, when a twenty-four hour specimen is not available for practical reasons, as in an out-patient department, it would be better to test a specimen of the urine passed early the same morning, and brought by the patient, than a specimen passed during the middle of the day. The early morning concentration would give a maximum figure, which would be fairly characteristic.

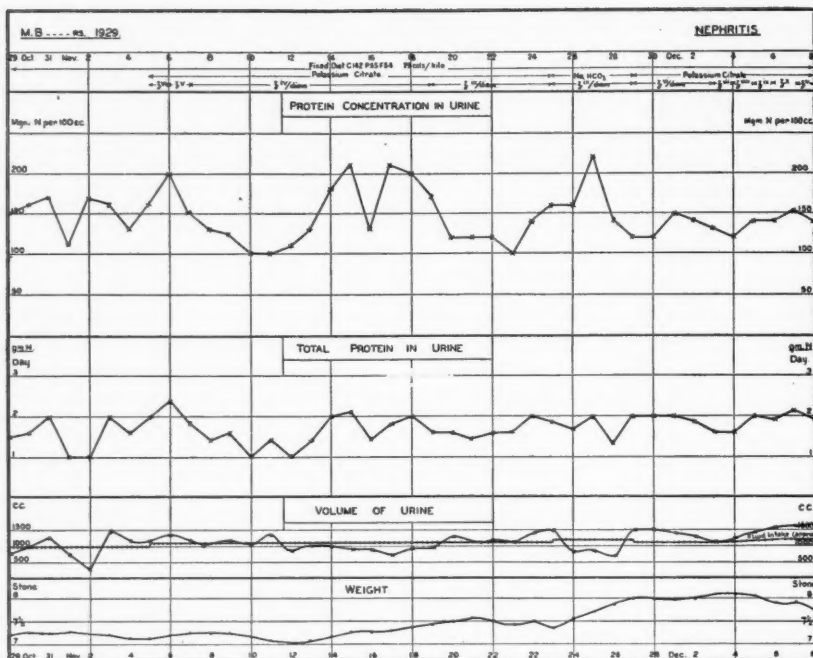


FIG. 5.

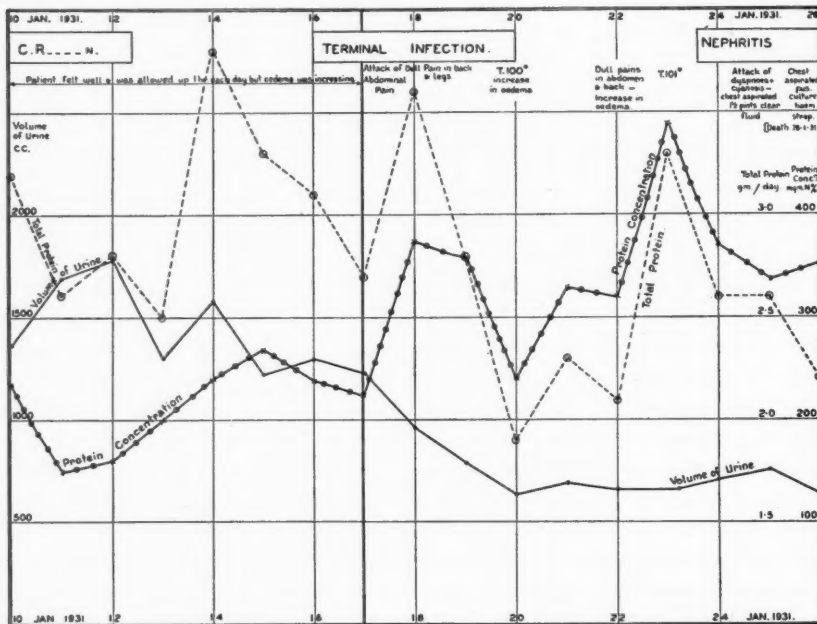


FIG. 6.

It is not intended to imply that the total daily protein loss has been found to be constant in any one patient. It does in fact vary considerably even in a patient in an apparently stationary clinical condition. But in those patients of whom records have been kept over months, it has been found that the limits between which the daily protein loss varies are characteristic of the patient's condition and the stage of the disease. An average of the protein loss on three consecutive days would give a reliable mean figure.

In conclusion I have to thank Professor Arthur Ellis for his interest and criticism and for encouragement to make these observations on his patients, Dr. Horace Evans, of whose clinical notes on these patients I have made use, the Medical Research Council for personal and expenses grants, and Mr. R. H. Ruse for technical assistance.

Summary

1. The concentration of protein in the urine of patients with nephritis has been shown to vary during the day. It is highest in the evening and early morning specimens. A moderate rise in concentration occurs in the middle of the day.

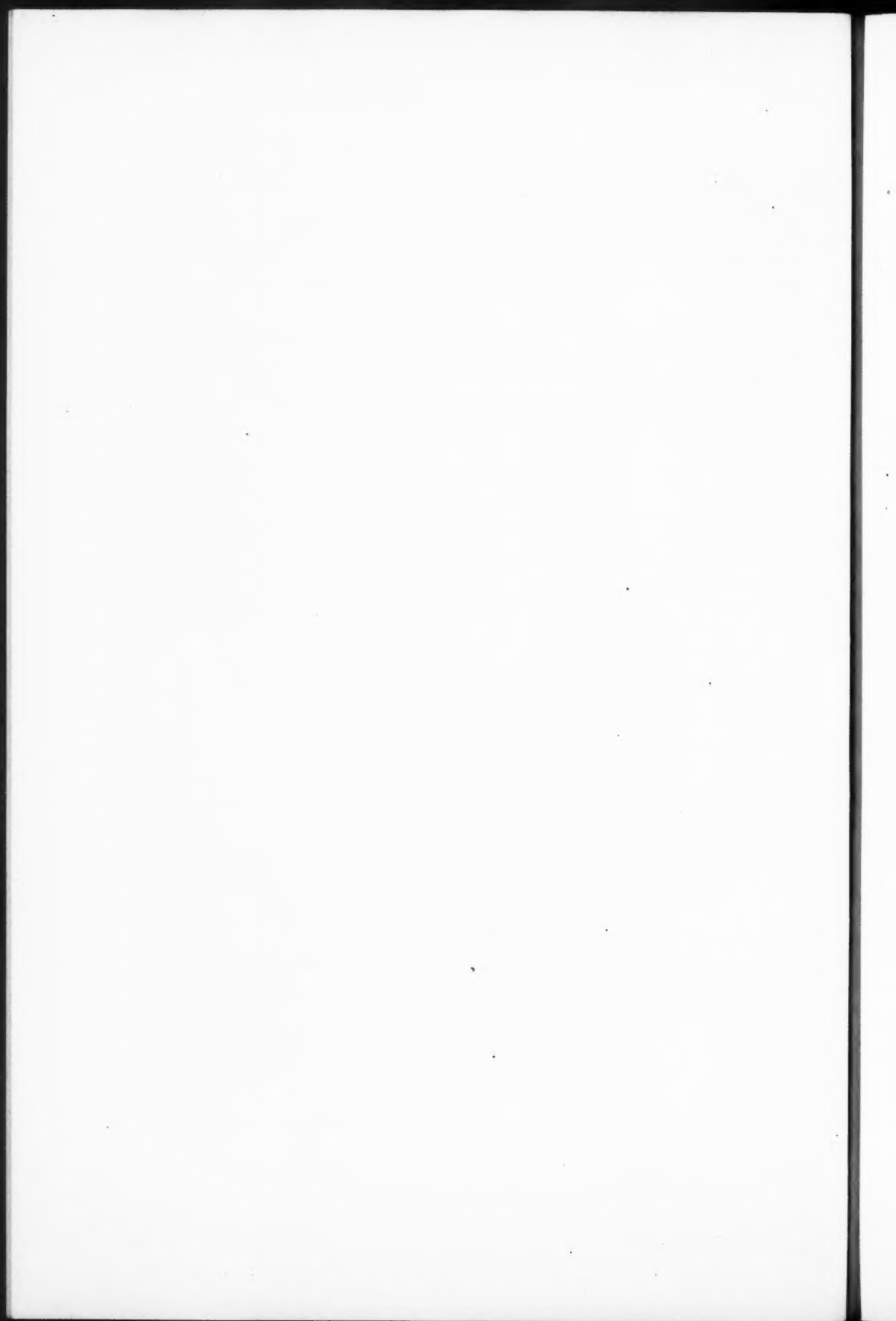
2. The total amount of protein lost is greater by day than by night, owing to the greater relative increase in the volume of urine passed during the day.

3. The effects of getting up from bed, of diuretics, and of infections, may cause large increases in protein concentration without change in the total amount of protein lost, on account of the simultaneous decrease in urine volume in inverse proportion.

4. It is suggested that the total protein loss per twenty-four hours is a more valuable clinical guide than the protein concentration in a single specimen of urine. When a twenty-four hour specimen is not available, the concentration of protein in an early morning specimen will give more useful information than that in a specimen passed during the day.

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SOME ASPECTS OF THE ELECTROCARDIOGRAM IN TOXIC GOITRE¹

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THERE is wide difference of opinion as to whether the changes in the heart which are often present in toxic goitre are irreparable, at any rate in part, or whether they may be temporary toxic phenomena which disappear completely with the successful treatment of the disease. In a recent paper Thomas (1) states that even the most severe intoxication from hyperthyroidism need not produce permanent functional cardiac damage: he quotes one patient who died of heart failure, and in which the post-mortem findings were of a negative nature. On the other hand, Strickland Goodall (2) appears to hold the view that in severe cases there must be permanent damage; he finds that there are bundles of necrosed muscle fibres scattered amongst apparently healthy fibres. Hamilton (3) regards rheumatic fever with cardiac damage as a predisposing cause to disorders of the heart in hyperthyroidism and stresses its relation to fibrillation.

While following up forty-two cases of toxic goitre which had been operated on, an electrocardiogram was done on thirty-six; the follow-up was at an average interval of just over three years after operation, and thirty-three were cases of Graves' disease, the remainder being cases of toxic adenoma as judged by the histology of the removed gland. The basal metabolic rate and the blood-pressure were recorded, and as twenty patients had already had electrocardiograms taken before operation we were able to see any changes which had occurred since operation and compare these with the blood-pressure and the basal metabolic rate.

All electrocardiograms were taken under carefully standardized conditions, the deviation being 3 cm. for 3 M.V. current against the patient's electrical resistance. They are therefore comparable. The electrocardiograms were taken by our assistant, Miss Nora C. Rogers, and the high standard of her work helped us considerably.

All investigations were undertaken after the patient had been in hospital and in bed for at least twenty-four hours. The blood-pressure was taken lying down, with a mercury manometer, and the basal metabolic rate was determined by the Douglas Bag and Haldane Gas Analysis apparatus, and these determinations form part of a series of 1,200 observations made in the past three and a half years.

¹ Received May 20, 1931.

Results

The outstanding feature of the electrocardiograms in our series taken at the time of the follow-up was the number of cases in which *T* was inverted in Lead 3, as in nine of the thirty-six patients *T* was found to be inverted. We were fortunate in having electrocardiograms of six of these cases before operation, but as the inversion was only present in two of these at that time, the change has taken place in the other four after operation. A letter was sent to each patient's private practitioner, as it was thought that the inversion might be due to digitalis, but in only one case was the patient receiving this drug, and she was taking 5 minims of the tincture three times a day.

A list of the basal metabolic rates and the blood-pressures in these nine cases yield the following readings:—

B. M. R.	Blood-pressure.
+ 20 %	150/85
+ 5 %	130/90
0	170/115
+ 6 %	116/70
0	144/100
0	145/90
—22 %	150/90
+ 2 %	No record
—16 %	148/98

It is clear that neither the basal metabolic rate nor the blood-pressure has any constant bearing on the inversion. In some cases the metabolism is normal, and in others it is either increased or below normal.

An inversion of *T* in Leads 2 and 3 was noted at the follow-up in two cases, in both of which it had developed since operation, as tracings taken before operation showed *T* to be upright, but one of these was the patient who was receiving 5 minims of tincture of digitalis three times daily; but it is not our experience that this is sufficient to invert the *T* wave. The opposite effect of operation was seen in two cases which had an inverted *T* in Leads 2 and 3 with spread and splitting of *R* before operation, and, at the follow-up, normal tracings with no inversion were recorded.

Hamburger (4) with others remarked on the tendency of *T* to become smaller in height and even to become inverted under treatment, and, as in his cases the *R-T* interval also increased, he suggested that the changes were due in part to variations in vagal and sympathetic tone. Increased vagal tone manifests itself by a slowing of the pulse and a shortened systole, while possibly increased sympathetic tone causes an increased pulse-rate and lengthened systole. We were unable to agree with Hamburger's suggestion in so far as it affected inversion, as the inversion occurred in the presence of both, as is shown in the following table:—

Case.	Time.	Pulse-rate taken from the E. K. G.	Q-T Interval.	Type of <i>T</i> ₃ Wave.
1	Before operation	108	7/25	Upright
	After operation	96	8/25	Inverted
2	Before operation	60	10/25	Upright
	After operation	96	7/25	Inverted

Both the patients were receiving iodine before operation. In Case 1 the inversion occurred after the pulse had slowed and the Q - T interval had lengthened, while in Case 2 the inversion took place with an increased pulse-rate and a shortened Q - T interval.

The R wave. Changes in the height of the R wave were seen frequently, as in many cases R was tall before operation and considerably diminished at the time of the follow-up. There were twenty cases in which the R wave could be compared. The actual measurement made was Q to R , and it was taken in Lead 2. In eleven cases before operation R was found to be over 23 mm. in height, the tallest being 32 mm., and in ten of these a surprising diminution in the height was seen at the follow-up, the average difference being 7 mm. and in one case 14 mm. One case showed an increase after operation of 6 mm., that is from 17 mm. to 23 mm. Particular cases could be singled out in which R diminished with the fall in the basal metabolic rate, but the height cannot always be predicted, even roughly, from the basal metabolic rate. In one case to which reference has already been made R was 17 mm. when the basal metabolic rate was +26 per cent., yet at the follow-up R was 23 mm. and the basal metabolic rate was -7 per cent. The relation of the height of R to the patient's electrical resistance was not calculated, but the variation of this factor in this disease is well known.

P and T waves and R-T interval. White (5) states that in hyperthyroidism T is often low and does not parallel the basal metabolic rate. Hamburger (4) with others found a high T wave in many of their cases before operation, and Krumbhaar (6) also calls attention to the well-developed T in toxic cases. Strickland Goodall (7) stresses the high P wave, and in his cases it reached the level of the T wave.

We have measured the height of T in twenty cases before operation, and of P in eighteen cases as two were fibrillating: if T or P were more than 3 mm. above the upper limit of the base line it was regarded as tall.

	Tall.	Well-developed.	Small or Inverted.
T	4	12	4
P	5	9	4

A comparison was also made between T and P . P was taller than T in eight cases, smaller in six, and equal in four. We were unable to find a constant parallel between the height of P or T and the basal metabolic rate, and we give a few examples which illustrate the variation seen.

B. M. R.	P in mm.	T in mm.
+27 %	—	7
+58 %	—	1
+57 %	5	—
+46 %	1.5	—

Nine of these twenty patients were traced a few days after their operation with the following results:—

T was unchanged in four, shorter in four, and taller in one case. P was unchanged in five, shorter in two, and taller in one case: in one case

fibrillation was present. There was no constant relationship between changes in P or T and a fall in the basal metabolic rate, but of course the number is small, and it is of interest that Krumbhaar (6) found that T became shorter after operation in eleven of twenty-three cases. Hamburger (4) with others also noted that when T decreased in size as a result of treatment this was associated with an increase in the $R-T$ interval. We measured the $R-T$ interval and found that it increased after operation by $1/25$ th to $2/25$ ths of a second in seven of nine cases, yet we did not find that it bore any close relationship to a fall in the height of T or P .

At the follow-up we compared P , T , and the $R-T$ interval with the tracings taken before operation. Amongst eighteen cases T had decreased in eight, and increased in four. P had decreased in seven, and increased in four. P was now taller than T in eight cases, smaller in four cases, and approximately equal in the remaining cases. Here again there was no uniform relationship between the basal metabolic rate and the height of either P or T . On measuring the $R-T$ interval we found that this had increased in fifteen cases compared with the pre-operative tracings, in some as much as $2/25$ ths of a second, decreased in two, and was similar in one. Since operation the $R-T$ interval had increased in four cases, decreased in two, and was similar in one. The basal metabolic rates in the two cases which had decreased were +20 per cent. and 0 respectively.

The $R-T$ interval usually increased as the toxicity of the disease diminished, as indicated by the basal metabolic rate and the general symptoms. We expected to find that it would always coincide with a fall in the pulse-rate, yet occasionally this relationship did not hold, and we now give a few examples to show, firstly, the degree of variation, and, secondly, that this is not dependent in all cases on the pulse-rate (e.g. Case 3).

Case.	$R-T$ Interval.	Pulse-rate on the E. K. G.
1	$5/25$	108
	$6/25$	96
	$7/25$	84
2	$4/25$	96
	$7/25$	48
3	$5\frac{1}{2}/25$	84
	$6\frac{1}{2}/25$	84

Dominance. Krumbhaar (6) found that six of his cases showed an increased left ventricular preponderance after operation, while in one case the preponderance became less. He had eleven cases of slight or marked right ventricular preponderance, and after operation five cases showed a diminished preponderance, three showed no change, and in two the preponderance was increased.

Ten of our thirty-six patients followed up had a left ventricular preponderance, in eight it was well marked and not always associated with an increased blood-pressure. One case with very well marked left ventricular predominance had a blood-pressure of 125 systolic, diastolic 80. Two patients

who showed only a slight dominance before operation at the follow-up had a marked dominance, yet the blood-pressures were systolic 142, diastolic 98, and systolic 150, diastolic 90, respectively: their basal metabolic rates were within normal limits, and the increase in dominance cannot be attributed to a persistence of toxicity. In only one case was a right dominance present.

Auricular fibrillation. Auricular fibrillation was present in four of the thirty-six cases; in one case it had developed since operation. In this case the basal metabolic rate was +59 per cent., and the condition is a recurrence rather than a persistence of the disease, as she was regarded as cured until she was involved in a fire.

In many recorded cases thyroidectomy produces a cessation of fibrillation, and those interested in this aspect are referred to papers by Hamilton (3), Phillips (8) and Anderson, Dunhill (9), Fraser, and Stott, and Hurxthal (10). Phillips and Anderson found that thyroidectomy brought about normal rhythm in 60 per cent. of cases. Hurxthal reports a higher percentage amongst selected cases.

Splitting of R. Splitting of *R*, sometimes with spreading, was present in more than Lead 3 in three cases at the time of the follow-up. It was associated in two cases with fibrillation, one being the case that had developed since operation, and in one case with a marked left dominance and a blood-pressure of systolic 144, diastolic 100. The splitting had developed in the last case since operation, and an inversion of *T* in Lead 2 was also present. In three cases splitting was present before operation and was not present at the follow-up.

We did not have any cases with undue prolongation of the *P-R* interval.

Myocardial damage. The criteria on which we have made a diagnosis of myocardial damage is evidence of one or both of the following:—

1. Spreading and splitting of the *R* wave in more than Lead 3.
2. Inversion of *T* in Lead 2.

Auricular fibrillation has not been regarded as evidence of myocardial damage.

On this basis there were four cases of myocardial damage at the time of the follow-up: two were cases in which auricular fibrillation was also present. In two of these four cases the damage was present before operation but has progressed, the basal metabolic rates are -22 per cent. and +59 per cent., and the blood-pressures are systolic 150, diastolic 90, and systolic 220, diastolic 80, respectively. Amongst the tracings which were done before operation there are three cases in which there was evidence of myocardial damage which at the time of the follow-up had quite disappeared. This represents the more gratifying side of the picture, and is to some extent more in line with clinical observations.

Summary

Our study of the *T* wave in Leads 2 and 3 led us to the conclusion that no opinion could be based upon its form as to the future of the case, nor could we find any alterations in the magnitude of the *T* or *P* waves or in the duration of the *R-T* interval which would help in an opinion as to the future history of the case. The size of *P* and *T*, relative or absolute, bore no constant relation either to the metabolic rate or the clinical condition of the patient. On the other hand, it was our experience that the height of the *R* wave frequently showed considerable reduction after operation, and it was thought that the explanation might lie in changes in the electrical resistance which would necessitate considerable variation in the tension on the Einthoven fibre. We found no constant relation between the height of *R* and the metabolic rate.

It is striking that a left ventricular preponderance occurred so frequently in our cases as compared with the rarity of right dominance, in view of the findings of Krumbhaar (6); age was not found to be a factor in our series.

Auricular fibrillation as recorded by us occurred in approximately 10 per cent. of the cases and was of the persistent type. No special investigation was made to record attacks of spasmodic fibrillation which were known to occur in some of the cases but of which we possess no graphic record, and we are inclined to think that cure of fibrillation of the established variety subsequent to operation is not easily accomplished even with intensive quinidine administration.

Our finding of progressing myocardial damage subsequent to a successful operation and reduction of metabolic rate associated with apparent clinical improvement would be more disturbing were it not for the fact that it occurred in only a small group.

Evidence is produced to show that electrocardiographic changes in toxic goitre may belong to any of three classes:—

(a) Toxic, transient, and recoverable—in these cases tracings before operation have shown undoubted signs of muscle change, but when repeated three or four years later presented a total absence of such abnormalities.

(b) Toxic changes which are found to still persist three or four years later, unchanged in degree, in spite of manifest benefit from the surgical treatment adopted.

(c) Changes which must be regarded as not only organic and permanent, but actually progressive in character, in spite of the apparent success resulting from treatment when judged from the purely clinical aspect.

Further, we have failed to find any data upon which an opinion could be based, as to the class to which any individual patient would ultimately belong, and such criteria as have been suggested by other workers found no constant counterpart in the series of cases which we have studied.

Our work has been not only facilitated, but very materially helped, by the co-operation of our surgical colleague, Mr. G. Jefferson, to whom we are indebted for the majority of the cases recorded.

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THE VENTILATION EQUIVALENT FOR OXYGEN¹

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With Plates 1 to 4

VARIOUS methods have at different times been suggested for expressing the ventilation efficiency of the respiratory apparatus by some simple formula, but up to the present no great popularity has been attained by any of these. It is essential that the results obtained for various subjects shall be directly comparable, and such figures as minute volume of respiration or vital capacity present certain difficulties. For example, the former depends on various factors, such as the state of tissue metabolism, while a certain degree of reduction of the vital capacity is compatible with perfectly efficient pulmonary ventilation at rest. Simonson (1) attempted to overcome some of these drawbacks with his 'caloric ventilation equivalent' which represented the minute volume of respiration per calories used, while Herbst (2) called the amount of oxygen retained by the body out of one litre of inspired air the 'utilization coefficient'. We have chosen for the purposes of this paper the formula first described by Anthony (3) as the 'ventilation equivalent for oxygen'. This represents the volume of inspired air that gives up 100 c.c. of oxygen to the body and is usually expressed in litres, i. e.

$$\text{Ventilation equivalent for oxygen} = \frac{\text{Minute volume of Respiration} \times 100}{\text{Oxygen used per minute}}$$

Such a formula excludes the dependence between pulmonary ventilation and oxidation processes, and the results obtained depend principally upon the efficiency of the pulmonary and circulatory systems. We believe that a study of the ventilation equivalent for oxygen throws some light upon the problems of dyspnoea, and with a normal circulatory system it represents a useful index of respiratory efficiency which may prove valuable in connexion with the modern developments of thoracic surgery.

Method

The estimation of the minute volume of respiration, and the amount of oxygen utilized by the body, has been carried out by means of the 'Knipping

¹ Received July 8, 1931.

Metabolism Apparatus' (4) which further provided us with an accurate graphic record of the respiratory movements of our subjects. This apparatus in its simplest form (see Plate 1, Fig. 1, *a* and *b*) consists of a gasometer with a capacity of eight litres, a glass flask, a small motor pump, and a three-way stopcock connected to the patient by a special rubber mouthpiece. By means of rubber tubing these four parts form a closed circuit in which a definite quantity of air can circulate. The patient inspires from (through the three-way stopcock) and expires into the apparatus. The expired air has to pass through a measured quantity of a solution of caustic potash and in so doing loses its carbon dioxide. A small glass filter plate in the path of the air as it passes through the caustic potash solution facilitates adequate absorption because of the numerous small bubbles produced. The diminution of the quantity of air in the system during the experiment is measured on a scale attached to the gasometer, and this is the quantity of oxygen consumed by the patient. Breathing into the apparatus is very easy, and in no way hindered, as the tubes connecting the patient and gasometer are wide and entirely free from valves or calcium chloride tubes. The free circulation ensured by the pump eliminates the question of dead space in the apparatus itself. The movements of the gasometer are registered in ink on a kymograph, the speed of which can be accurately regulated by means of a special clockwork attachment. The gasometer is filled with air or oxygen at the beginning of the experiment, and fresh oxygen can be added if required during the experiment. The use of this apparatus for spirometric work is fully described by Anthony (5). From the curve registering the breathing it is possible to work out the minute volume, oxygen consumed per minute, average tidal air, &c. Plate 2, Fig. 2 represents a typical normal curve. This must be read from left to right, the curve rising evenly during the experiment as oxygen is absorbed from the circulating air in the apparatus. Inspiration is represented by the upstroke, expiration by the downstroke, and each horizontal division represents 200 c.c. (With the simplest form of the apparatus each division represents 100 c.c.) Each vertical division on this curve represents one minute, but this speed can be varied by means of a specially constructed kymograph, which also makes possible a sudden shunt to a quick rate in order to produce an exact respiration curve for detailed study. This is shown towards the end of the normal curve here illustrated. The base line joining the lowest part of the curve at each respiration remains absolutely straight during the experiment, and unless this is present the curve cannot be regarded as correct. Accurate measurement of the curve gives the various factors required to calculate the ventilation equivalent.

For the purpose of obtaining normal controls we have investigated the ventilation equivalent of over fifty completely normal subjects. These were, for the most part, medical colleagues, laboratory workers, or medical students. Convalescent patients were not considered as presenting sufficient normality for the purpose of this investigation. The experiments were

carried out with the subjects fasting, either first thing in the morning with no breakfast, or about noon after a light breakfast at 8.0 a.m. The subject was kept lying quietly for about half an hour before the experiment, and in certain instances, where the apparatus was strange or any nervousness was expected, a preliminary test investigation was carried out. The gasometer of the apparatus was filled with purified oxygen obtained from the usual oxygen gas-cylinder and passed through caustic potash solution, a sulphuric acid-potassium bichromate mixture, turpentine, granulated charcoal, and silicic acid. Preliminary experiments with air, ordinary oxygen, and purified oxygen had shown no material difference in the results obtained, and purified oxygen was selected for the experiments as having a more definite standard value. The subjects breathed in connexion with the apparatus for one or two periods of ten minutes. In certain instances the amount of carbon dioxide expired was estimated by titrating the caustic potash solution at the end of the experiment. It was thus possible to calculate the respiratory quotient and the basal metabolism as additional checks upon the complete normality of the subjects investigated. Rigorous attention to experimental detail is essential in this work, and it is particularly important to secure complete mental calm for the subjects, as any degree of nervousness increases the minute volume. Study of the respiratory movements on our tracings enabled us to detect cases of such irregular or nervous breathing, and in such cases repeat investigations were carried out. We calculated the ventilation equivalent for at least three, and usually for each of the ten minutes, taking the average as the normal for the subject under investigation. Correction for normal temperature and pressure is unnecessary, as the factor would appear both in the numerator and the divisor of the equation.

Results

From the study of our normal subjects the following results were obtained. The material comprised 54 adults of whom 31 were males and 23 females. The average age in years for males was 29.4 (limits 22 to 60) and for females 26.2 (limits 17 to 42). The total number of experiments carried out was 81 and the average ventilation equivalent for all controls was 2.44 litres calculated according to Anthony's formula already quoted. The limits, however, were somewhat wide, being 1.68 to 3.7 litres. There were six subjects with equivalents over 3, and it was not possible to repeat in these cases. Since repetition would almost certainly have produced a lowering in these high values we feel justified in excluding them from this series, and this gives us the average figure of 2.37 litres with limits of 1.68 to 2.89, representing a normal variation of approximately ± 25 per cent. There was no apparent difference in the results according to sex, and the differences according to age are grouped in the following table.

Age.	Number of Controls.	Ventilation Equivalent. Litres.	Limits.
Under 20	2	2.40	2.38-2.42
20-25	20	2.38	1.69-3.70
26-30	17	2.37	1.68-2.89
31-35	10	2.59	2.08-3.59
36-40	1	2.11	—
Over 40	4	2.49	1.81-3.49

It will be seen that so far as these comparatively small numbers go there is no appreciable relationship between age and the ventilation equivalent.

This normal figure for the ventilation equivalent for oxygen of approximately 2.4 litres is lower than that obtained by Anthony in his original investigations. He found a value of 2.75 litres, but his limits were considerably wider than ours, namely, 2 to 4.5 litres. In a later work Knipping and Arsenijević (6) found the ventilation equivalent for oxygen lying between 1.8 and 3.6 litres, which approximates nearer to the present results. The reasons for such wide variations are not altogether clear, but the more placid the individual the lower the value obtained in most cases, while a nervous subject usually gave higher figures. Indeed, one subject actually slept while being investigated, and the calming influence of sleep is shown by the fact that while his 'waking' value for the ventilation equivalent for oxygen was 2.5 litres, this dropped as low as 1.29 litres during a sleeping period of a few moments' duration (Plate 2, Fig. 3). The importance of nervous factors is also shown by the influence of morphia upon the equivalent (see below).

Individual variations also occur in normal subjects, but these can be eliminated to a large extent by ensuring that the conditions of the investigation as regards time of day, temperature of the room, &c., are kept constant. Daily variations for three subjects are shown here. (Ventilation equivalent for oxygen given in litres.)

Subject.	Consecutive Days.						Average.	Limits.	Variation per cent.
	1	2	3	4	5	6			
M.	2.58	2.43	2.87	2.53	2.66	2.35	2.57	2.35-2.87	+11.6 - 8.5
A.	1.76	2.03	2.03	2.08	1.94	2.09	1.99	1.76-2.09	+ 5 -11.5
L.	1.68	1.78	2.09	2.04	2.05	—	1.93	1.68-2.09	+ 8.2 -13

Continuous investigations over longer periods than ten minutes have not been possible with the apparatus used by us, nor are these necessary for the purpose of determining the ventilation equivalent for individual subjects. We have, however, calculated the equivalent from the minute volume of the respiration and the amount of oxygen consumed by normal human subjects in certain of the classical metabolism experiments by Magnus-Levy (7). For example, in an investigation with a fasting subject ('W') lasting for twenty-four hours, the ventilation equivalent for oxygen lay

between 2.09 litres and 2.91 litres with an average for the whole period of 2.5 litres. There was a rise in the value of the equivalent at the times in the day when a meal would normally have been taken, e.g. between 1 p.m. and 2 p.m. and again between 7 p.m. and 8 p.m., which serves to emphasize the influence of emotion on the equivalent. Other experiments from this same investigation after various types of food gave similar results, showing in general very little variation for the individual under conditions of quietude. Four such experiments are here summarized.

Type of Food.	Duration of Test.	Average Ventilation Equivalent. Litres.	Limits.
Fat	9½ hours	2.31	2.13-2.47
Carbohydrate	5 "	2.12	2.00-2.32
Protein	8 "	2.23	1.88-2.53
Full diet	11 "	2.76	2.59-3.03

Effects of exercise. Although complete quiet is necessary for the investigation of the ventilation equivalent, this is not because movement as such tends to increase it. Properly conducted exercise in a normal individual increases both the minute volume of respiration and the oxygen consumed per minute in a parallel fashion, and hence the ventilation equivalent for oxygen remains unaltered. This is well shown in an experiment described by Douglas and Haldane (8), which, although conducted for another purpose, gives sufficient data as regards minute volume of respiration and oxygen consumed to enable us to calculate the ventilation equivalent for oxygen.

Conditions of Work, &c.	Oxygen Consumed per minute.	Minute Volume of Respiration.	Ventilation Equivalent for Oxygen.
	c.c.	c.c.	Litres.
Rest in bed	237*	7670*	3.24
Rest—standing	328*	10,400*	3.17
Walking			
2 m.p.h. laboratory	668	16,300	2.44
2 " grass	780	18,600	2.38
3 " laboratory	907	20,900	2.30
3 " grass	1,065	24,800	2.33
4 " laboratory	1,182	29,000	2.45
4 " grass	1,595	37,300	2.34
4½ " laboratory	1,493	34,200	2.29
4½ " grass	2,005	46,500	2.32
5 " laboratory	2,125	51,300	2.41
5 " grass	2,543	60,900	2.39

* Said to be high normal values in original paper.

The table indicates that during exercise the values for the ventilation equivalent only varied between 2.29 and 2.45 litres.

We have also calculated the ventilation equivalent during exercise from data obtained by other workers in this clinic in the course of ergometric experiments. (The methods of measuring the gaseous exchange and the amount of work performed have been elsewhere fully described by one of us—H. W. K. (9)). In three normal subjects work performed by pedalling

a fixed bicycle had no appreciable effect on the ventilation equivalent for oxygen except in subject 'W', where an abnormally high resting value became normal during exercise. The values for rest in these cases were obtained with the subject sitting on the bicycle after a preliminary resting period on a couch.

Subject.	Ventilation Equivalent at Rest.	Ventilation Equivalent during Exercise.	Work performed in Watts
	Litres.	Litres.	per second.
W	3.26	2.63	52.1
Hei.	2.31	2.31	50.5
Her.	2.10	2.26	63.6

The constancy of the ventilation equivalent during exercise in healthy subjects should be compared with the increase taking place in patients with disease of the heart or lungs, to be described below.

Influence of inspired air. It has already been mentioned that, broadly speaking, we found no difference in the equivalent whether the gasometer was filled with air, oxygen from an oxygen cylinder, or purified oxygen. It should be remembered, however, that filling the gasometer in the apparatus here used with pure oxygen does not mean that the subject will be inspiring pure oxygen, for the dead space of the apparatus, in the rubber tubes, glass flask, pump, &c., serves to dilute this to a percentage varying with the size of this dead space and the amount of gas in the gasometer. Obviously, if very little oxygen is run into the gasometer at the beginning of an experiment the pressure of this gas in the inspired air will quickly drop below that of atmospheric air, and may even reach dangerous limits. Similarly, if distilled water is substituted for caustic potash in the glass flask, the carbon dioxide expired will accumulate in the apparatus. We have studied the effect of oxygen-poor air and carbon dioxide-enriched air upon the ventilation equivalent both in dogs and in human subjects. Breathing with air in which the oxygen gradually becomes less and less the minute volume of respiration increases, while the amount of oxygen consumed per minute shows only a slight rise. Thus with subject 'W' (Plate 2, Fig. 4) after ten minutes breathing the oxygen in the apparatus was reduced from approximately 20 per cent. of the total volume to 5 per cent. The ventilation equivalent for oxygen for the same period rose from 2.5 litres to 4.21 litres, and after the addition of oxygen to the apparatus to bring the percentage by volume up to over 20 the equivalent sank to 1.65. The same subject breathing with air in which the carbon dioxide was allowed to accumulate showed the well-recognized increase in the depth of respiration with increased minute volume, and the ventilation equivalent for oxygen rose correspondingly: e.g. with 2.5 per cent. by volume of carbon dioxide in inspired air the ventilation equivalent for oxygen was 2.27 litres, while with 6 per cent. of carbon dioxide it was 4.23 litres. Similar results were obtained from dogs under avertin anaesthesia (Plate 3, Fig. 5). These observations

on the effect of lack of oxygen or excess of carbon dioxide on the breathing confirm those of many previous observers dating from the classical observations of Haldane and Priestley (10) in 1905. The present experiments were carried out in order to obtain figures for the ventilation equivalent for oxygen under these conditions.

The ventilation equivalent for oxygen in disease. In diseased conditions the ventilation equivalent for oxygen is altered in various ways according to the type of respiration present and other factors. For the most part the cases here to be discussed suffered from dyspnoea, using this term in its broadest sense, and hence it will be convenient to describe them in three main groups according as to whether the dyspnoea is due to (a) alterations at the respiratory centre, (b) alterations in the circulatory system, or (c) alterations in the respiratory system. This cannot be regarded as a hard and fast classification, however, for as Fraser (11) has shown, for example, cardiac dyspnoea is essentially due to stagnation in the blood-flow about the respiratory centre. The grouping will serve, nevertheless, to illustrate the alterations in the ventilation equivalent for oxygen, and the more extensive problem of dyspnoea is to be considered by us in another paper in the light of the present and other investigations still in progress.

Alterations at the respiratory centre. The effect of nervousness on the part of the subject under investigation has already been mentioned. Obviously a nervous tachypnoea will increase the minute volume out of proportion to the increase in oxygen consumption per minute, and thus the ventilation equivalent for oxygen will be abnormally high. Reduction in the equivalent towards normal is always obtained at a second investigation in such patients. Stimulation of the respiratory centre is best seen in diabetic coma, and a very characteristic respiration-curve is obtained in this condition (see Plate 3, Fig. 6). The minute volume of respiration is very greatly increased and the ventilation equivalent for oxygen is also very high: in one of our cases it reached 11.4 litres, and two days later, after effective treatment, this had sunk to 3.1 litres. The equivalent is also abnormally raised in the precomatose stage and tends to be above normal long after any objective evidence of ketosis remains on clinical examination. This very high ventilation equivalent for oxygen is very characteristic of diabetic coma, as Arsenijević and Knipping (6) have shown. In uraemic coma we have found also a raised ventilation equivalent for oxygen, but not to the same extent as in diabetes. In one patient, aged 62, semi-conscious, with a systolic blood-pressure of 225 mm. Hg., suffering from uraemia, we found the respiration more rapid and deeper than normal with a ventilation equivalent for oxygen of 4.85 litres. Such patients, however, usually have some alteration in the circulatory system as an additional factor.

Depression of the respiratory centre during sleep has already been mentioned above as producing a lowering in the ventilation equivalent for oxygen. A certain amount of 'nervous inhibition' of respiratory movement is also seen in certain cases of intra-abdominal inflammatory trouble,

and this also leads to a lowering of the equivalent. This is illustrated by a patient, aged 25 years, with acute cholecystitis, who breathed in a slow and irregular fashion, and gave a ventilation equivalent for oxygen of 1.4 litres. The most striking effects of depression of the respiratory centre, however, are seen in cases of poisoning by morphia and other sedative drugs. In one patient, aged 42 years, with acute morphia poisoning after 0.4 grm. of morphia had been taken, the ventilation equivalent for oxygen was only 1.25 litres (see Plate 4, Fig. 7, *a* and *b*). In order to stimulate the respiratory centre the carbon dioxide produced was not absorbed in caustic potash solution as usual, but allowed to accumulate in the apparatus during the investigation. After five minutes the breathing had become much deeper, and in the sixth minute the equivalent had risen to 1.78 litres with between 5 and 6 per cent. of carbon dioxide by volume in the inspired air. Intravenous injection of lobeline (0.003 grm.) greatly stimulated the respiration, bringing the equivalent to the normal value of 2.81 litres. The patient was reinvestigated six days later, after complete recovery, and the ventilation equivalent was then 2.57 litres. Similar depressive effects on the respiratory centre were seen in a case of veronal poisoning, with a ventilation equivalent for oxygen of 1.4 litres, and in luminal poisoning of 1.73 litres. In these unconscious patients it has been necessary to use a special mask in place of the usual rubber mouthpiece.

Alterations in the circulatory system. The ventilation equivalent for oxygen in patients with cardiac failure is raised roughly in proportion to the degree of failure present. Thus the highest value in the cases investigated up to the time of the writing of this paper (17 in number) was 8.61 litres in a patient aged 66, with very severe dyspnoea and evidence of serious myocardial damage after coronary thrombosis. On the other hand, in a patient with auricular fibrillation, well compensated and without dyspnoea the normal value of 2.1 litres was obtained. An old man of 76 years with severe congestive failure showed the classical Cheyne-Stokes type of respiration on the curve obtained and the calculated ventilation equivalent for oxygen was 4.43 litres. The cardiac failure cases are grouped in the accompanying table (see p. 25), where a rough classification under 'slight', 'moderate', or 'marked' degree of failure is noted. After a few days' rest in bed and treatment directed towards the heart failure the equivalent tends to move towards normal. Thus in one young patient with mitral stenosis, admitted after recent haemoptysis, a value of 3.62 litres for the ventilation equivalent had become 2.98 litres after three days.

These results are only in accord with what has already been frequently reported by other workers as regards pulmonary efficiency in cardiac failure cases, and the ventilation equivalent merely supplements clinical observation as to the degree of dyspnoea, &c., present. It does, however, give a definite numerical indication of pulmonary efficiency comparable to the result of estimating the blood urea, for example, in certain types of renal failure. Further, by means of this ventilation equivalent it is possible to

study closely the effect of exercise upon patients with pathological lesions of the heart.

Ventilation Equivalent in Patients with Heart Disease

Patient.	Sex.	Age.	Diagnosis.	Degree of Failure.	Ventilation Equivalent in Litres.	Remarks.
G.	F.	34	Auricular fibrillation	None at rest	2.1	Recent cerebral embolus
C.	F.	61	Aortic aneurysm	None at rest	2.46	No dyspnoea at all
H.	F.	55	Mitral stenosis	None at rest	2.25	
B.	M.	51	Mitral stenosis	Slight	3.47	Recent lung infarction
T.	F.	19	Mitral stenosis	Slight	2.79	Slightly propped up
—	—	—	Same patient	—	2.90	Flat in bed
S.	F.	45	Aortic aneurysm	Slight	2.09	Respirations somewhat difficult
K.	M.	26	Mitral stenosis	Slight	3.62	? mechanical
—	—	—	Same patient	—	2.98	Recent haemoptysis
						After three days' rest in bed
W.	F.	71	Auricular fibrillation	Moderate	3.03	
K.	F.	81	Auricular fibrillation	Moderate	4.74	
H.	F.	80	Myocardial degeneration	Moderate	3.58	High blood-pressure
O.	F.	62	Myocardial degeneration	Moderate	3.35	High blood-pressure
A.	F.	52	Mitral incompetence	Moderate	3.03	Moderate hypertension
H.	F.	46	Chronic nephritis	Moderate	3.30	High blood-pressure
W.	F.	37	Mitral stenosis	Moderate	3.90	
G.	F.	71	Auricular fibrillation	Marked	4.72	
S.	F.	66	Myocardial degeneration	Marked	8.61	Old coronary thrombosis
E.	M.	76	Myocardial degeneration	Marked	4.43	Cheyne-Stokes breathing; died next day

It has already been pointed out that in normal subjects the effect of exercise is to increase the minute volume of respiration and the oxygen consumption in a parallel fashion so that the ventilation equivalent for oxygen remains the same. In patients with cardiac disability this mechanism breaks down, the minute volume increases out of proportion to the oxygen consumed, and the ventilation equivalent rises. This is well shown in the following ergometry experiment carried out for us by Miss Rüttgers, for whose help we are very grateful in this and certain other of the ergometric experiments to be quoted below.

The patient was a man, aged 50, with syphilitic aortic incompetence, with no dyspnoea nor other evidence of cardiac failure at rest (lying), when his ventilation equivalent was as low as 1.66 litres. He performed his exercise by turning a handle attached to an electric dynamo for three minutes, the work done being recorded electrically. The effect upon his ventilation equivalent is shown as follows:

Time of Experiment.	Respiratory Rate.	Oxygen Used. c.c.	Minute Volume. c.c.	Ventilation Equivalent. Litres.	Work Done. Watts per sec.
Standing before experiment	17	360	12,040	3.35	—
Second minute of work	27	680	33,960	4.99	38.8
Third minute of work	27	680	39,970	5.88	38.8

It is well recognized that in the early stages of cardiac failure dyspnoea may only be present on exertion, and this rise in the ventilation equivalent for oxygen in such patients represents, we believe, a valuable method of indicating this clinical observation in a more exact manner.

In anaemia, the carrying power of the blood for oxygen becomes considerably diminished and the normal gaseous exchange between pulmonary capillaries and alveoli is interfered with. The amount of pulmonary ventilation necessary to obtain 100 c.c. of oxygen for the body becomes increased, and this is shown in our cases of pernicious or severe secondary anaemia by the raised ventilation equivalent for oxygen. Exercise also produces an increase in the equivalent in these cases, and the effect of even twenty-four hours' rest in bed is shown, for example, in the patient 'W' in the following table where an equivalent of 6.16 litres on admission had become 3.58 by next day. The cases of anaemia in our series are shown as follows:

Patient.	Sex.	Age.	Type of Anaemia.	Hb. per cent.	Colour Index.	Ventilation Equivalent. Litres.
G.	M.	45	Pernicious	22	1.5	3.63
W.	F.	53	Pernicious	30	1.1	6.16
Same patient 24 hours later						
R.	F.	75	Secondary	22	1	3.50
M.	F.	58	Secondary	64	1.2	4.17

Alterations in the respiratory system. In acute disorders of the lungs and bronchi it is technically difficult to obtain satisfactory respiratory tracings, and consequently the cases of pneumonia, for example, in this series, are small in number. In two men, aged 32 and 41, with pneumonia, but with a good general condition, we obtained figures for the ventilation equivalent for oxygen of 3.29 litres and 3.83 litres respectively. This rise in the equivalent was associated with a rapid shallow type of respiration which, as Meakins (12) has shown, is a most inefficient type of breathing.

In tuberculous patients the alteration in the ventilation equivalent

depends upon various factors, principally concerning the type and extent of disease, the degree of toxicity, and the mechanical effects on the respiratory movements. An investigation of thirty-one cases of acute and subacute pulmonary tuberculosis, all hospital in-patients, gave an average ventilation equivalent for oxygen of 3.28 litres but the limits were wide and individual variation was also wider than normal. A young patient, aged 16, with acute pulmonary tuberculosis, with high fever, gave an equivalent of 3.74 litres, the high value in this case being associated with an obviously marked degree of tachypnoea. As an isolated 'test' in cases of pulmonary tuberculosis, the determination of the ventilation equivalent has no particular value, but a consideration of the changes produced in the equivalent by pneumothorax and by exercise suggests possible lines of future investigation.

We have reckoned the ventilation equivalent for oxygen from respiratory curves made for the purpose of other investigations by Anthony in this clinic from patients with pulmonary tuberculosis before and after artificial pneumothorax treatment had been instituted. The alterations in the equivalent after a pneumothorax had been induced varied with the time elapsing between the pneumothorax and the obtaining of the respiratory tracing. In general, where tracings were made on the same day before and after a pneumothorax, we found that an abnormally high equivalent was reduced to normal limits after the operation, a reduction varying from 25 to 40 per cent. Where a greater interval existed between the investigations such a decrease was not seen, and it appeared likely from the few cases investigated that the immediate decrease is followed by a slow return to the previous high level, which may be exceeded. The results obtained in typical cases are shown in the following table:

Patient.	Sex.	Age.	Ventilation Equivalent.		Interval between Pneumothorax and 2nd test.
			Before * in Litres.	After in Litres.	
W.	M.	18	4.65	2.77	Same day
B.	M.	33	3.25	2.43	Same day
G.	M.	32	3.75	2.32	Same day
B.	M.	23	2.97	1.99	Same day
D.	M.	29	3.61	3.02	3 days
				3.60	6 days
H.	M.	22	4.50	3.00	2 days

* On same day as operation.

There is obviously scope for further investigation of this problem, especially as regards the effects of refills, &c. The fact that immediately after a pneumothorax normal ventilation of the lungs is present, as indicated by the normal equivalent, is yet another point in favour of collapse therapy in pulmonary tuberculosis, and the value of the ventilation equivalent in association with modern forms of thoracic surgery demands study in the future.

In association with exercise, tuberculous patients show variations in the

ventilation equivalent analogous to those shown by cardiac patients already mentioned (Plate 4, Fig. 8). In other words, among patients still undergoing treatment in hospital for pulmonary tuberculosis, for whom at rest the ventilation equivalent for oxygen was normal, the effect of exercise was to increase the equivalent, showing that the normal mechanism of pulmonary ventilation had not yet made its reappearance. This result is shown in three typical cases taken from an investigation by Miss Rüttgers (13) in this clinic.

Patient.	Before Work—Standing		At Work—3rd Minute		Work in Watts per second.
	Minute volume	Ventilation Equivalent.	Minute volume.	Ventilation Equivalent.	
	c.c.	Litres.	c.c.	Litres.	
Ha.	8,370	2.09	26,360	3.06	42.2
Ho.	9,715	2.37	22,060	2.56	42.4
S.	8,090	2.13	31,420	3.65	52.7

In certain cases of asthma investigated in collaboration with Dr. William Lewis we found the ventilation equivalent to be somewhat irregular. The inclusion of asthma in this group of respiratory disorders is perhaps incorrect; it might be strictly better to consider the results under central nervous disturbances but, as said at the outset, the classification here used is not meant to be absolute. Broadly speaking, in a small series of patients with asthma, the results fell into two groups: high equivalents, such as 5.65, 4.10, and 3.70 litres in three patients or low equivalents such as 1.96, 1.62, 1.73, 1.81, 2.08, 2.10 in six patients. The clinical conditions of these patients was in keeping with the equivalents found. In the former group with raised ventilation equivalents for oxygen the patients were of a particularly anxious type, breathing rapidly and difficultly with a high minute volume. In the second group with low or low-normal equivalents such obvious mental distress was absent; respiration was still difficult, but was slower and more deliberate, the minute volume being reduced. The influence of adrenalin in various forms (inhalation of an 'atomized' solution in glycerin, injection subcutaneously of pure adrenalin solution, or of various proprietary preparations) was to bring the ventilation equivalent back towards normal in association with the subjective relief experienced: the high equivalents were diminished and the low equivalents increased by the adrenalin therapy. This is shown diagrammatically in Fig. 9, where the values for the ventilation equivalent in asthma are grouped about a line indicating the approximate normal of 2.5 litres. The value before treatment is shown at the base of the arrow, while the point of the arrow represents the value immediately after adrenalin therapy.

Metabolic disorders. It was stated at the outset of this paper that the use of Anthony's formula for the ventilation equivalent for oxygen made the results obtained independent of the great metabolic processes of the body. Hence the raised equivalents found in cases of pulmonary tuberculosis, for example, are not due to the increased oxygen consumption and increased minute volume which are the accompaniments of the metabolic

processes of fever. This is well illustrated by a patient investigated, who had erysipelas and a temperature of 104°F . The minute volume was increased to 9,480 c.c. and the oxygen consumption to 300 c.c. per minute, giving, however, only a slightly raised equivalent of 3.16 litres which, since the patient was 73 years old, can probably be regarded as a high normal.

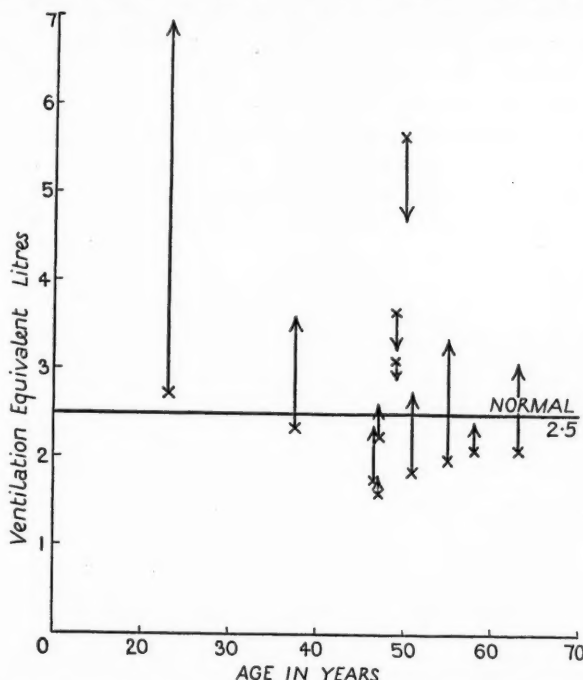


FIG. 9. Effect of treatment with adrenalin on the ventilation equivalent in asthma.

Similarly in exophthalmic goitre the increased metabolic rate does not influence the ventilation equivalent, for oxygen, provided the circulatory apparatus, for example, is functioning normally. In ten patients with Graves' disease investigated for this we found an average equivalent of 2.70 litres.

Summary

1. The ventilation equivalent for oxygen is defined as the volume of air which has to be inspired in order that 100 c.c. of oxygen shall be obtained by the body (Anthony).

2. In normal subjects its value is approximately 2.4 litres, and under experimental conditions remains unaltered after food or on moderate exercise. It is raised by emotional influences, lowered in sleep, and considerably increased if the carbon dioxide or oxygen content of the inspired air is varied outside physiological limits.

3. In pathological conditions the ventilation equivalent for oxygen is altered according to various factors. Thus depression of the respiratory centre (e.g. morphia poisoning) causes a decrease, and stimulation of the centre (e.g. diabetic coma) causes an increase in its value. In disease of the circulatory and respiratory systems the equivalent is raised roughly in proportion to the degree of failure in the normal function of these systems.

4. The equivalent appears to give a good indication of the state of pulmonary efficiency, and its determination may prove of value in connexion with the development of thoracic surgery.

5. The type of dyspnoea present in diseased conditions may be elucidated to a certain extent by a determination of the ventilation equivalent for oxygen, which appears to give a rapid method of distinguishing between diabetic coma and morphia poisoning, for example, and in diabetic coma serves the further purpose of giving a delicate indication of the degree of ketosis present.

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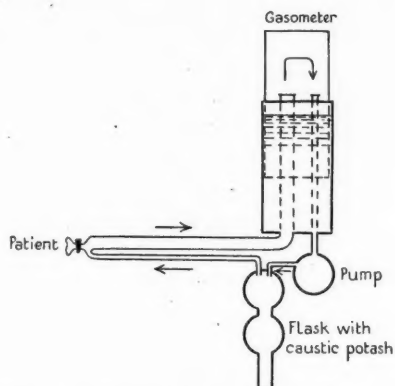


FIG. 1 a. Diagram to show the main parts of the Knipping apparatus

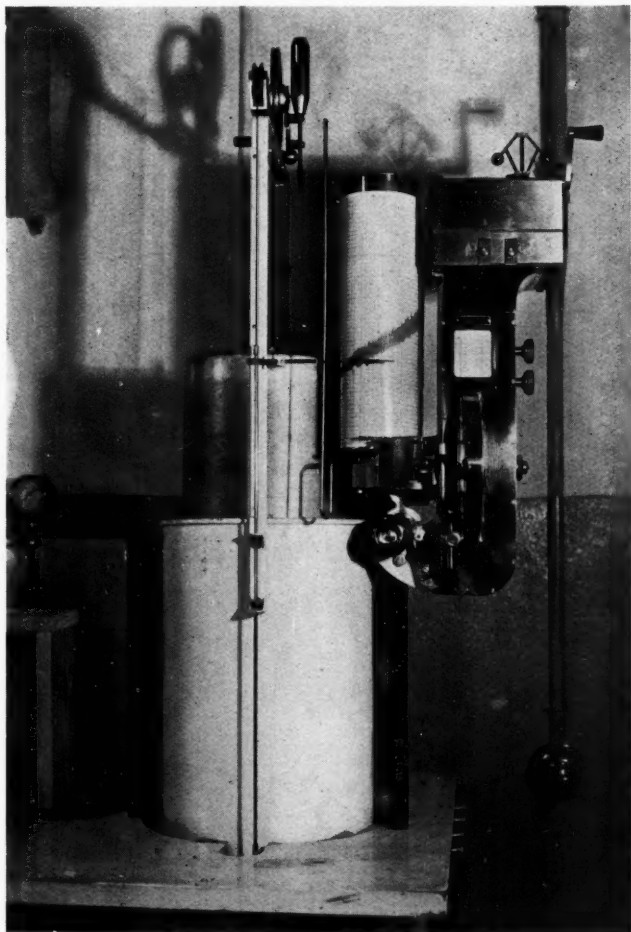


FIG. 1 b. Photograph of the gasometer and kymograph of the Knipping apparatus. The kymograph here shown is more elaborate than that on the ordinary apparatus and permits wide variations in speed

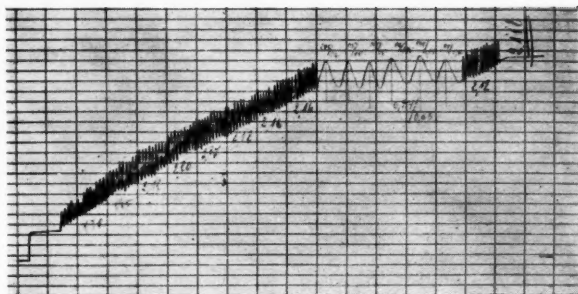


FIG. 2. Normal respiratory tracing. To be read from left to right. Each horizontal division = 200 c.c. Each vertical division = 1 minute. Upstroke = inspiration. Down-stroke = expiration.

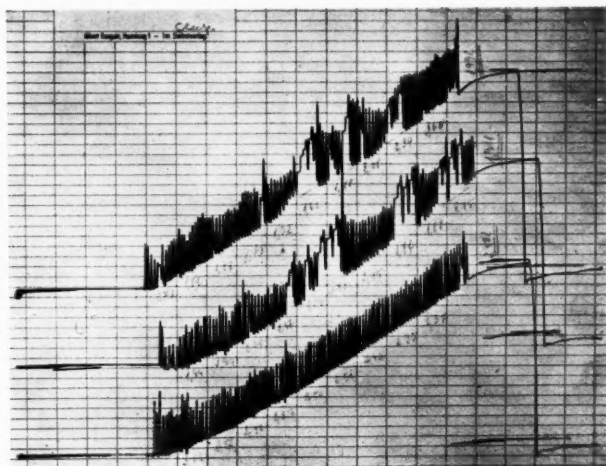


FIG. 3. Effect of sleep on respiration shown in the irregular portions of upper two tracings. Horizontal division = 100 c.c.

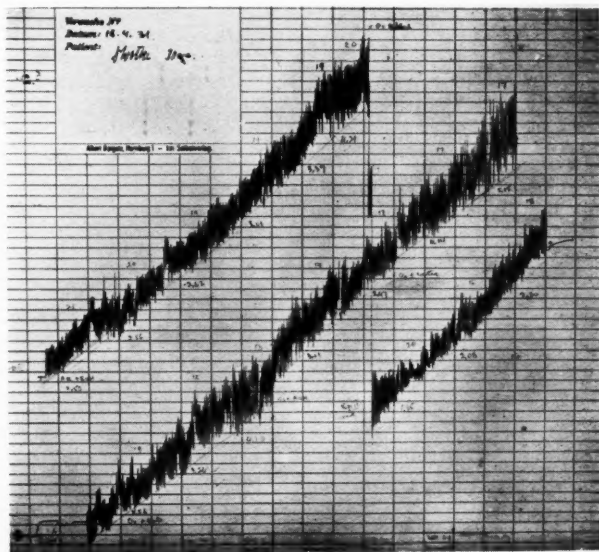


FIG. 4. Uppermost tracing shows effect of diminished oxygen on the breathing: oxygen added and tracing continued at lowest level. Middle tracing shows effect of allowing carbon dioxide to accumulate in apparatus. Horizontal division = 100 c.c.

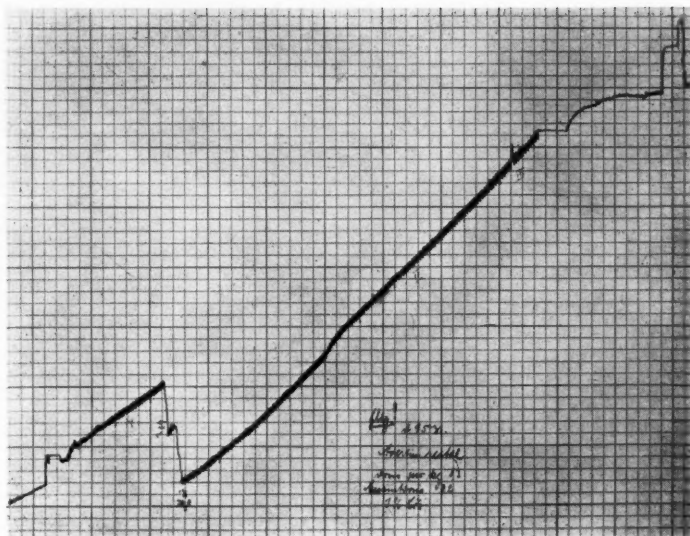


FIG. 5. Effect of carbon dioxide in inspired air on dog under avertin anaesthesia. Increase in depth of respiration is seen towards end of curve. Horizontal division = 100 c.c. Three vertical divisions = 1 minute.

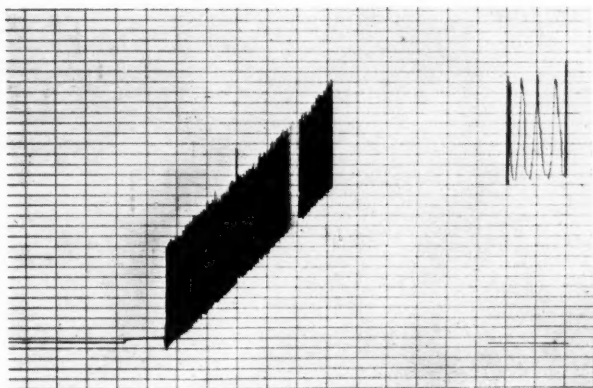


FIG. 6. Typical respiratory tracing in diabetic coma—deep and rapid. Horizontal division = 100 c.c. Vertical division = 1 minute.

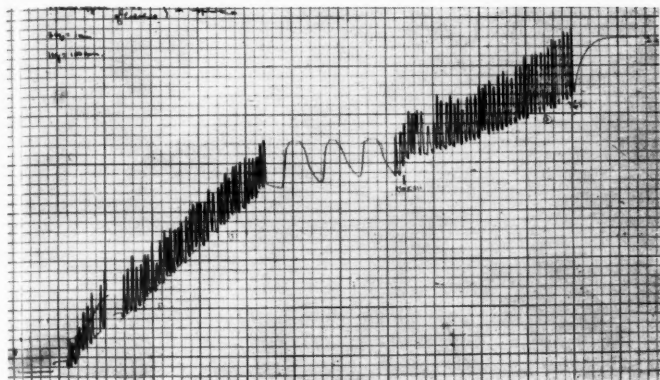


FIG. 7a. Respiratory tracing in morphia poisoning, showing stimulating effect of CO_2 in latter part.

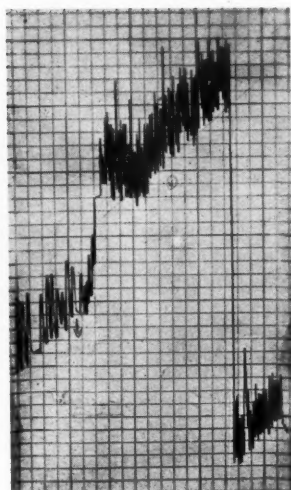


FIG. 7b. To show effect of lobeline on the same patient: breathing deeper and quicker. Horizontal division = 100 c.c. Three vertical divisions = 1 minute.

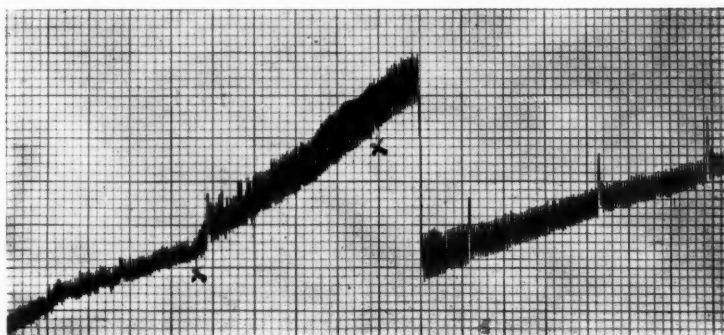
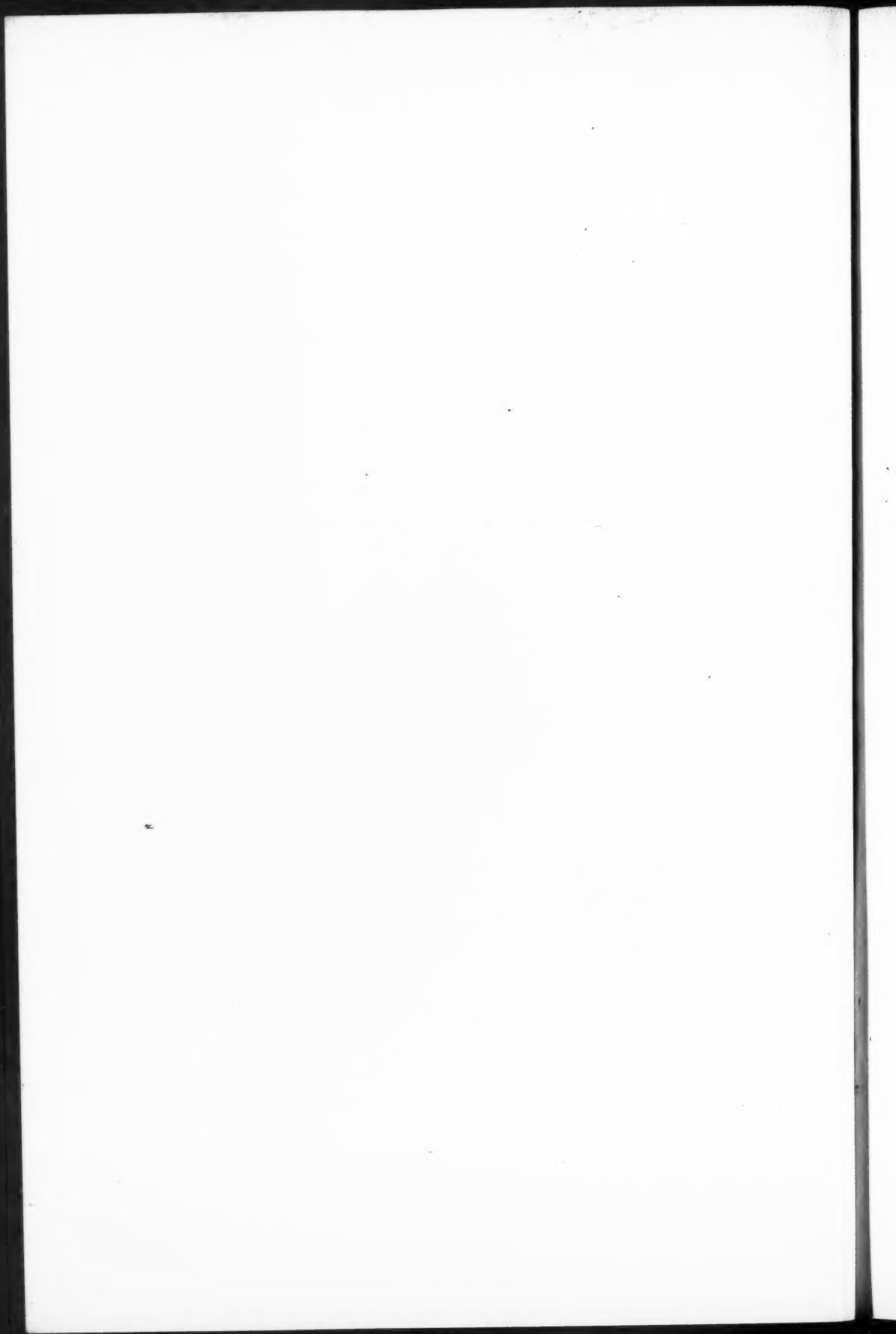


FIG. 8. Effect of work on the respiratory tracing in tuberculosis: work for 3 minutes between X and X. Horizontal division = 200 c.c. Seven vertical divisions = 1 minute.



THE OCCUPATIONAL INCIDENCE OF PRIMARY LUNG CANCER¹

By WILLIAM BROCKBANK

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THE aetiology of primary cancer of the lung is as obscure as is the aetiology of most cancers, but it presents a number of interesting problems which, in view of its increasing incidence, merit the greatest attention and study. Trauma, the inhalation of irritant dusts and fumes, bacterial and toxic agents (influenza, syphilis, tuberculosis, and bronchitis), and hereditary predisposition have all been suggested and considered as major aetiological factors.

Amongst the dusts, ordinary house dust, road and trade dusts, have been implicated, while, amongst the fumes, tar, petrol, radioactive gases, gaseous arsenical compounds, irritant vapours in chemical plants and laboratories, poison gases, and even tobacco smoke, have all been cited as aetiological factors. Only four of these seem to warrant serious consideration:— (a) tuberculosis, which Ewing (7) believes to be the chief aetiological cause; (b) influenza, as suggested by Barron (1); (c) chronic bronchitis (Ravdin (24)); and (d) the inhalation of irritant substances, which has been freely discussed since the pulmonary affection which had been known for generations to affect workers in the Schneeberg mines of the Erzgebirge in Saxony was shown by Härting and Hesse in 1879 (10) to be due to malignant tumours of the lungs. The disease, which is preceded by pneumokoniosis, affected a small group of men who all followed the same occupation; lung tumours were not abnormally prevalent in the population of the neighbourhood.

A remarkable fact was observed by Schmorl (26) in making a detailed study of the disease. Among the cases investigated were four men who had been employed for a long time in the Schneeberg mines, but had given up work on account of lung trouble. It was not until between ten and eighteen years later that they developed the cancer from which they died. Schmorl 'can scarcely assume that the lung cancer had developed during the time of their employment in the mines, and, since an accidental incidence of lung cancer such as occurs in other people is not specially likely, we must conclude that during their work as miners they acquired the cancer-exciting factor, which, however, remained inoperative in them for a very long time'.

¹ Received April 20, 1931.

The Schneeberg mines are eight in number and extend to a depth of 1,500 yards, and from them cobalt, bismuth, and arsenic are obtained. The air in the mines is radioactive, possessing an emanation content up to 50 Mache units. In the drilling of the hard rock great quantities of dust are produced containing minute sharply-angled particles with an arsenic content reaching 0.45 per cent.

Cobalt and bismuth are mined elsewhere without the occurrence of the disease, and in many occupations where pneumokoniosis is known to occur there does not appear to be an unusual incidence of lung cancer. The arsenical content and radioactivity of the dust have received the greatest attention, and attempts to produce lung cancer in mice by inhalation of Schneeberg drill dust have had no success (25).

Other substances have been used by many workers in an attempt to produce lung cancer in animals. Particular attention has been given to tar and its products, for both clinically and experimentally skin cancer is known to follow chronic irritation with tar. Möller (20) observed primary lung cancer in six out of twenty-four rats following the painting of their backs with tar. These results were confirmed by Murphy and Sturm (21), who applied tar to a number of separate areas of the skin of mice in such a fashion that no single area was irritated sufficiently long to cause lesions of the skin. They obtained a high incidence of lung tumours (60 per cent. in one series and 78.3 per cent. in another). Control mice failed to show a single instance of such growths. The tumours were epithelial neoplasms. This experiment was repeated by Smith (29), using petrol instead of tar. Out of twenty-nine mice one developed a lung cancer. Bonne (2) also noticed a higher incidence of lung tumours in mice after the applications of tar to the skin.

Tar fumes failed to produce a single tumour in Smith's mice, but Kimura (15) has successfully produced an adenocarcinoma of the lung in one out of ten guinea-pigs and one out of three rabbits by the intratracheal injection of crude coal tar, an experiment that was not confirmed by Bonne.

Various other dusts and fumes have been used. Smith produced lung cancer in one out of twenty-six mice exposed to motor-exhaust gases. Willis and Brutsaert (31) found tumour-like structures of the bronchial mucosa of seven out of eighty guinea-pigs subjected to the prolonged inhalation of silica dust. Similar structures had never been obtained by them in an extensive experience of experimental studies of the lungs in other guinea-pigs.

The experiments of Winternitz, &c. (32), have been repeatedly misquoted. They produced epithelial proliferation in the bronchi following intra-bronchial insufflation of weak acids. This proliferation was not cancerous as has frequently been stated.

In assessing this work it is important to take into account the spontaneous occurrence of primary neoplasms of the lungs and bronchi in animals. Such

tumours have been discovered in the lower animals in a wide range of genera. In particular, attention has been directed to their occurrence in mice since Livingood (19) first described the condition. Most of these tumours have been shown to be adenomatous and not carcinomatous.

Pneumonokoniosis has often been recorded in connexion with lung cancer, and in consequence the occupational incidence of the disease has become important.

TABLE

Labourers	170
Unspecified but dusty occupations	137
Housework	120
Clerks	52
Manual workers	48
Carpenters	28
Builders	22
Metalworkers, tailors &c.	18
Vanmen	16
Cigar manufacturers	15
Butchers, masons, shop assistants, tradesmen	13
Travellers	12
Chauffeurs	10
Bakers, chemists, painters, seamen	8
Gardeners	7
Agents, tram-men	6
Blacksmiths, bottleblowers, engineers, farmers	5
Gasworkers, grooms, miners, nurses, railway-workers	4
Coalsellers, cooks, doctors, engine-drivers, policemen, schoolmasters, silversmiths, weavers	3
Bankers, clockmakers, combmakers, fishermen, officers, plumbers, postmen, schoolboys, silk manufacturers, slaters, washerwomen	2
Actress, bailiff, book-keeper, broker, butler, cardboard manufacturer, cement worker, cheesemaker, cobbler, cooper, dairy manager, dancer, demolisher, director, draughtsman, dustman, employer, elevator-man, factory hand, fireman, gold-beater, iceman, janitor, longshoreman, milkman, mill owner, museum attendant, musician, overseer, paperhanger, pensioner, piledriver, potter, presser, printer, publican, reporter, scientist, soldier, street-sweeper, street messenger, tanner, warehouseman	1

It seemed that an investigation of the occupations of the published cases might throw some light on the problem, and therefore 898 cases have been collected from the literature. All these were proved *post mortem*, and there does not appear to be a doubt about the diagnosis of any one of them. The occupations are given in the accompanying table. It will be observed that no one occupation stands out, but one gets the impression that the labouring classes are especially predisposed and that the professional classes are relatively immune.

Unfortunately, adequate study of the occupational incidence of the disease has not been made: the recurrence of the word 'labourer' is ample evidence of that. The writer remembers a man who died of lung cancer who gave his occupation as a storekeeper, but closer investigation showed that he had only held that post for a few months, having for twenty-five years previously been a cement-carrier. The study of the influence of work can only be made by obtaining a detailed occupational history from the time of the patient's apprenticeship, for it must not be forgotten that one of the

Schneeberg miners took eighteen years to die from the disease. How careful this inquiry must be is illustrated by Orr's patient (22) who died of lung cancer. The history gave the patient's occupation as that of an actor with no apparent dust hazard. Repeated inquiries brought no enlightening information until the particular form of acting was discussed, when it was learned that he was a buck dancer, and for twenty-five years had scattered sand on the stage before dancing.

Simpson (28) also records a man who described himself as a jeweller, but further inquiries elicited the fact that he worked with a machine that bevelled down the gold in a sand-paper process that resulted in a dusty atmosphere heavily laden with minute particles.

The following sixty-two patients of the Manchester Royal Infirmary have been studied in this way. The notes are not by any means complete, many details having been missed through lack of knowledge of industrial disease. Each patient seemed to be a definite case of primary lung cancer on clinical and radiological grounds, but unfortunately not all of them could be examined pathologically.

Male Cases

Case 1. Died aged 47; prior to the war a wine and bottle merchant—afterwards a Civil Service clerk.

Case 2. Died aged 47; occupation unknown till aged 30, sack carrier at a potato wharf; 33 to 36, fruit salesman; 36 to 37, horse carter; 37 to death, warehouseman—'a dusty job'.

Case 3. Died aged 17; bread van boy.

Case 4. Died aged 58; loader on the railways all his life—principally meat and hides from the abbatoirs—complained of fumes from the hides.

Case 5. Died aged 56; aged 24 to death, attended to the gas-lights of railway carriages.

Case 6. Died aged 49; buyer of printed cotton goods.

Case 7. Died aged 30; apprenticed into the electrical trade; aged 21 to death, a transformer test engineer.

Case 8. Died aged 59; aged 14 to 33, farm-hand; 23 to death, railway carter.

Case 9. Died aged 50; aged 13 to 37, puddling (steel) furnaces; 37 to 39, cupola (brass) furnace; 39 to 44, steel smelter; 44 to death, navy—excavator—for nine months prior to death was digging through garbage.

Case 10. Died aged 51; aged 13 to 28, piecer; 28 to death, spinner.

Case 11. Died aged 52; gentlemen's outfitter all his life—gas instructor during the war—never badly gassed, but often went into gas-filled room without mask.

Case 12. Died aged 46; wood-carving machinist all his life—mostly teak.

Case 13. Died aged 50; aged 23 to 48, horse carrier of cement; 48 to death, storekeeper.

Case 14. Died aged 64; aged 22 to death, tape sizer.

Case 15. Died aged 49; aged 14 to 20, foundry moulder; 20 to death, greengrocer.

OCCUPATIONAL INCIDENCE OF PRIMARY LUNG CANCER 35

Case 16. Died aged 57; aged 27 to 36, carter; 36 to 44, engine tender: 44, washerman; 44 to death, drain cleaner, used to go down fummy man-holes.

Case 17. Died aged 56; clerk all his life.

Case 18. Died aged 55; to aged 40, grey cloth storekeeper; 40 to death, linotype worker.

Case 19. Died aged 57; fish salesman all his life.

Case 20. Died aged 57; commercial traveller all his life; first groceries, then wines and spirits, and finally for a chemist.

Case 21. Died aged 41; engineer all his life—first at cotton mill, later (from aged 28) at a calico-printing works.

Case 22. Died aged 50; aged 26 to 46, clerk, first in an office—later in a granary; 46 to death, open-air canvassing.

Case 23. Died aged 42; aged 16 to 36, groom; 36 to death, chauffeur.

Case 24. Died aged 53; horse carter (newspapers) all his life.

Case 25. Died aged 46; to aged 34, horse carter; 34 to death, smelter (steel).

Case 26. Died aged 54; commercial traveller (confectionery).

Case 27. Died aged 63; commercial traveller (confectionery).

Case 28. Died aged 54; decorator and painter all his life.

Case 29. Died aged 55; aged 13 to 41, making-up bundles in a cotton mill; 41 to death, iron turner.

Case 30. Died aged 53; stonemason all his life.

Case 31. Died aged 29; aged 20 to 24, clerk; 24 to death, book salesman—gassed in the war.

Case 32. Died aged 46; aged 13 to 24, cabinet-maker; 24 to death, coffin maker.

Case 33. Died aged 64; many years to aged 52, boiler repairer; 52 to death, driver of coal-driven locomotive.

Case 34. Died aged 44; furniture salesman all his life—badly gassed in the war.

Case 35. Died aged 47; to aged 37, café manager: 41 to death, insurance clerk—badly gassed in the war.

Case 36. Died aged 49; commercial traveller all his life (cotton goods)—badly gassed in the war.

Case 37. Died aged 41; plumber all his life.

Case 38. Died aged 57; to aged 23, cab-driver; 23 to death, engine-cleaner.

Case 39. Died aged 64; aged 9 to 16, collier; 16 to 54, labourer at an iron works; 54 to death, furnace tender.

Case 40. Died aged 53; aged 13 to 20, clerk; 20 to death, rubber stockman.

Case 41. Died aged 63; pipe-fitter all his life—working in man-holes.

Case 42. Died aged 63; gas-works blacksmith all his life.

Case 43. Died aged 47; aged 15 to 23, working in sewers; 23 to 34, tiler 34 to death, post office engineer—often complained of fumes.

Case 44. Died aged 48; smelter all his life.

Case 45. Died aged 49; iron turner all his life.

Case 46. Died aged 66; coal miner all his life.

- Case 47.* Died aged 25; iron turner all his life.
- Case 48.* Died aged 47; moulder all his life.
- Case 49.* Died aged 55; aged 15 to 38, butcher; 38 to death, engine coaler.
- Case 50.* Died aged 60; first school attendance officer, then rate collector.
- Case 51.* Died aged 59; aged 15 to 44, porter at dye-works; 44 to death, travelling representative.
- Case 52.* Died aged 37; aged 13 to 22, dye-worker; 22 to death, goods porter.

Female Cases

- Case F 1.* Died aged 60; aged 15 to 18, stripper at a tobacco factory; 18 to 35, winder; 35 to death, housework.
- Case F 2.* Died aged 29; milliner all her life.
- Case F 3.* Died aged 71; housework for the last thirty years.
- Case F 4.* Died aged 42; housework all her life.
- Case F 5.* Died aged ?; housework for forty years.
- Case F 6.* Died aged 49; aged 18 to 28, telephone operator; 28 to death, housework.
- Case F 7.* Died aged 48; aged 14 to 24, hemmer in umbrella cover factory; 24 to death, housework.
- Case F 8.* Died aged 64; housework all her life.
- Case F 9.* Died aged 48; aged 23 to 39, teacher; 39 to 47, dispenser; 47 to death, teacher.
- Case F 10.* Died aged 23; aged 14 to 16, collar hand and ironer; 16 to 18, housework and cinema attendant; 18 to 19, laundry hand; 19 to death, housework.

In each case the occupation given by the patient was the one he was pursuing at the time he entered hospital. In Cases 9, 13, and 22 this was very misleading, whilst in several cases the important details were not given; for instance, Case 5 described himself as a railwayman, whereas he actually attended to the gas supplies of the carriages.

The list of occupations even when investigated on these lines does not bring to light anything very conclusive. Nine (14.5 per cent.) seem to have had definitely dusty jobs (12 and 32 carpenters, 13 cement carrier, 22 granary clerk, 28 decorator and painter, 30 stonemason, 33 driver of coal locomotive, 37 plumber, and F 2 milliner), whilst eighteen (29 per cent.) worked amongst gases and fumes (5 gas worker, 7 transformer test engineer, 9, 25, 44 smelters, 29, 45, 47 iron turners, 38 engine-cleaner, 39 furnace tender, 41 pipe-fitter (man-holes), 42 blacksmith, 43 post office engineer, 46 coal miner, 48 moulder, and 49 engine coaler, also in all probability 4 and 16).

Four of the patients were gassed in the war. This point is of interest in view of Kraus's (17) suggestion that the increase of lung cancers since the war may possibly be due to poisoning by war gases, as the disease preponderantly affects the males.

The question of tobacco smoke as a possible aetiological cause has been

discussed. Brinkmann (5) and Enger (6) have described cases amongst cigar workers, whilst four of Hunt's (13) twenty-six cases and one of Scott and Forman's (27) four gave a history of excessive tobacco smoking. Katz (14), on the other hand, does not consider this an important factor, and points to the Orient, where inhaling is common and lung cancer rare.

In my series nine (14.5 per cent.) smoked excessively, six smoking thick twist, whilst thirteen (21 per cent.) never smoked at all.

The question of the importance of road dust and motor-car fumes has received much attention, for it has been pointed out that the increase of traffic, and in particular of motor traffic, coincides with the increase of lung cancer. It has been suggested that the inhalation of dust and exhaust gases damages the bronchial epithelium and so starts the formation of cancer. Katz believes that both are important aetiological factors, and has the impression that town dwellers are in the majority and country dwellers relatively immune. This is confirmed by Folger and Materna's (8) statement that street animals are more subject to lung cancer than are pasture animals. Heilmann (11) and Brandt (4) blame the industrial contaminants of the air of large cities, whilst Staehelin (30) and Hampeln (9) incriminate the road dust, the latter pointing to Oslo as a city particularly free from dust, which shows a very low incidence of lung cancer.

To the contrary, Konrad (16) cites the town of Riga, where the disease is increasing without an increase of road tarring or of motor-cars; Probst (23) and Boyd (3) have not observed any special incidence amongst chauffeurs or garage workers, in fact most of the latter's cases come from the country districts of Western Canada, where contamination of the air by exhaust gases is negligible, and Holzer (12) points out that dust has not so suddenly increased as to explain the increase of lung cancer.

Lastly, Lehmann (18) has determined the tar content of the air raised from tarred streets by the passage of motor vehicles over them. His results suggest that the amount is too small to make the tarring of streets a factor of any importance in the aetiology of the disease.

In my own series seven (11.3 per cent.) were commercial travellers and van-men (3, 20, 24, 26, 27, 36, 51).

Conclusions

1. An investigation of the occupations of 898 cases of primary lung cancer collected from the literature suggests that the labouring classes predominate, although no one occupation stands out.

2. Poison war gas, tobacco smoking, road dust, and motor-car fumes are all possible aetiological factors.

3. The occupations of sixty-two cases have been investigated in some detail. Nine (14.5 per cent.) seemed to have definitely dusty jobs, and eighteen (29 per cent.) worked amongst gases and fumes. Four were badly gassed in the war, and nine smoked excessively.

4. A plea is made for more detailed investigation of the occupations of patients suffering from this disease.

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ANAEMIA WITH DYSPHAGIA¹

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ATTENTION was first drawn in 1914 to a peculiar type of dysphagia by Plummer, who called it a hysterical dysphagia. In 1918 Dan Mackenzie (3), Brown Kelly (6), and Paterson (9) all described cases of this type, in which definite pathological changes were present in the oesophagus. They pointed out that the dysphagia was easily cured by the passage of a large bougie. In 1922 Vinson (11) called attention to the constant association in these cases of a severe anaemia of the secondary type. Since then Moersch and Conner (8), Hurst (5), Ryle (10), Mason Jones (7), and Witts (12) have all published series of cases belonging to this group, while an excellent account of the condition was recently given in 1928 by Munro Cameron (1) in this Journal. He described the chief points of the syndrome in the following words: 'glossitis with atrophy of the oral and pharyngeal mucosa, definite reduction in haemoglobin percentage and some diminution of the red corpuscles, frequent enlargement of the spleen, and the symptoms of dysphagia referred to the region of the larynx, loss of appetite, debility, and nervousness.' The evidence so far brought forward suggests that the disease is primarily one of the mucosa of the mouth, pharynx, and oesophagus, with resulting dysphagia, and that the anaemia is secondary to the deprivation and restriction of food which necessarily follow.

We have studied five patients in whom the syndrome of dysphagia and anaemia was fully developed and one in whom all the signs were present with the exception of the dysphagia. The observations which we have made on these patients suggest the possibility of another explanation.

Our patients conform to the usual type in that they were all women; the average age of the five with dysphagia was 41, while the one without dysphagia was aged 33. The appearance of these patients was characteristic and striking. While the mucous membranes were pale, suggesting the presence of anaemia, the complexion in four cases showed the peculiar brownish-yellow colour seen in these cases. This differs distinctly from the lemon-yellow colour of pernicious anaemia, and persists for a long time after the anaemia has disappeared.

Five out of six patients complained of soreness of the tongue. In two patients, the tongue was completely bare of papillae; in two others, the

¹ Received September 1, 1931.

papillae were absent from the sides, while in one, soreness of the tongue, not at first associated with any visible change, was followed during a relapse by a complete loss of papillae. In the remaining patient, the tongue appeared normal and no complaint of soreness was made. The same patients with tongue affection also showed soreness and cracking of the corners of the mouth. The condition seen on oesophagoscopy similarly varied considerably in the five patients in whom this examination was made. In one case a web was seen by Mr. Bedford Russell, and there were areas of patchy oedema which bled easily when touched. In the other four, the mucosa appeared markedly pale. Examination by a barium meal was carried out in all cases; in five no abnormality was seen, while in the remaining case a slight delay occurred at the cardiac orifice, but this was not found on re-examination. The degree of anaemia present was marked, in two cases being very severe, with a haemoglobin figure of 33 per cent. and 36 per cent. respectively, while the remaining four showed less than 50 per cent. In each case it was of the secondary type, with a low colour index, and in the first two cases this was confirmed by means of a Price-Jones curve.

As the colour of the skin of the first case studied had suggested a tentative diagnosis of pernicious anaemia, a fractional test meal was carried out. This showed the presence, as in that condition, of an achlorhydria. The other five patients were therefore examined in the same way, and in each case with a similar result. Moersch and Conner (8) have also reported that eight out of ten of their patients showed an achlorhydria; in Witts's series (12) a fractional test meal was performed on seven patients, of whom four showed an achlorhydria, while in one only was the gastric secretion normal. On the other hand, Munro Cameron (2) found free HCl in the gastric contents of nine out of twenty-five patients, in whom a tube could be passed. The amount of acid was very small in the one case for which figures are given. D. T. Davies (4) has pointed out that many patients with achlorhydria after a gruel meal may be able to secrete hydrochloric acid after the additional stimulus of a subcutaneous injection of histamine. Thus out of fifteen patients with secondary anaemia and achlorhydria, nine had no free hydrochloric acid after histamine while the remaining six did excrete a little acid. This re-examination after histamine was not made in our cases. Although there is no unanimity of opinion about the presence of achlorhydria it seems probable that partial or complete achlorhydria is an important part of the syndrome.

The most important new point in the pathological findings concerns the fragility of the red cells. The patient (vi) who did not complain of dysphagia was admitted with the diagnosis of pernicious anaemia. When our house physician, Dr. J. Attwood, found that the blood-count was that of a secondary anaemia, he asked one of us (R. S. J.) to test the fragility of the red cells because he thought he could feel the spleen, and this, together with the brownish-yellow colour of the skin, and the severe secondary anaemia, suggested a possible diagnosis of acholuric jaundice. The corpuscles were

found to be definitely more fragile than usual, as haemolysis began in 0.55 per cent. saline solution, and was almost complete in 0.45 per cent. while the control (R. S. J.) showed no haemolysis in concentrations higher than 0.45 per cent. Further investigations, however, showed that the diagnosis of acholuric jaundice could not be sustained, for the blood serum contained no excess of bilirubin, achlorhydria (not a feature of the disease) was present, and on the clinical side there were in addition cracking and soreness of the corners of the mouth and atrophy of the papillae at the sides of the tongue. Moreover the colour of the skin resembled that of the other patients previously seen. In view of the unexpected result the fragility of the red cells was again tested both by R. S. J. and by Dr. H. E. Archer, fresh saline solutions being made up so as to exclude any source of error. As a further control, two patients with known acholuric jaundice were also tested on the same day. The initial findings were confirmed, an increase in fragility of the red cells being always present on this and on subsequent examinations (Table I). Moreover the red cells of other patients with severe secondary anaemia were also tested but showed no increased fragility.

TABLE I
Estimations of Blood Fragility: Case VI. (WS.)

		Saline %.							
		0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70
26/10/29									
	Patient (Hb. 45 %)	—	—	—	+	—	—	—	—
	Control A	—	—	+	—	—	—	—	—
7/11/29									
	Patient	++++	++++	+++	++	+	—	—	—
	Control B	++++	+	—	—	—	—	—	—
30/11/29									
	Patient (Hb. 48 %)	++++	++++	+++	++	+	—	—	—
	Control C	++++	+++	++	trace	—	—	—	—
17/12/29									
	Patient	++++	++++	+++	++	+	—	—	—
	Acholuric jaundice	++++	++++	++++	++	+	—	—	—
	Acholuric jaundice	++++	++++	++++	++++	+++	++	+	—
	Control A	++++	+++	+	trace	—	—	—	—
1/5/30									
	Patient (Hb. 58 %)	++++	++++	++	+	—	—	—	—
	Liver 6 months								
	Control A	++++	+++	+	—	—	—	—	—

Note : ++++ = Complete haemolysis (no red cell deposit visible).
 +++ = Marked haemolysis (marked red tint with deposit).
 ++ = Partial haemolysis.
 + = Slight haemolysis.

The technique used for this examination was briefly as follows. The saline solutions were freshly prepared for each case by dilution of a standard 1.0 per cent. NaCl solution with distilled water, to give dilutions of from 0.35 per cent. increasing by increments of 0.05 per cent. to 0.70 per cent.

NaCl. The red cells, collected from capillary blood, were subjected to a preliminary washing in normal (0.85 per cent.) saline solution, and a constant dilution of blood ensured by adding 0.1 c.c. of the washed and centrifugalized R.B.C. suspension to a constant volume (4 c.c.) of saline solution of appropriate strength. Each tube was then mixed by inversion and its contents allowed to settle, results being read and recorded conveniently in from three to four hours. 'Complete haemolysis' indicated absence of any red cell deposit, while less extensive haemolysis was shown by varying degrees of deposit of red cells and of red coloration of the supernatant fluid.

It was thus established that the red cells of the first patient examined were definitely more fragile than normal, the results being given in Table I. We therefore recalled to hospital the other five patients and examined them in the same way (Table II). Four out of the five, tested by independent observers, showed a definitely increased fragility, but one failed to show any increase: she had, however, already improved very considerably on liver feeding, the haemoglobin having risen from 32 per cent. to 70 per cent. at the time of the test. A Van den Bergh test done in three of these five patients gave a normal result. One patient (v) who showed a definitely increased fragility in April 1930 was readmitted to hospital in February 1931 with a return of the dysphagia and loss of tongue papillae and with only 38 per cent. of haemoglobin. On this occasion, however, the fragility of the R.B.C. was normal.

Other points. The menstrual history is not without possible significance in these cases. Two patients had complained of menorrhagia for five years or more before admission to hospital; in addition one had had a salpingo-oophorectomy four years previously and another a miscarriage with considerable haemorrhage one year and nine months before admission. Two of the patients, though not complaining of any menstrual irregularities, had many attacks of diarrhoea with, in one case, marked flatulent distension of the abdomen for periods of four and two years respectively. In one of these patients a sigmoidoscopic examination was made by Mr. J. E. H. Roberts, who reported a marked pallor and dryness of the mucous membrane of the sigmoid colon, similar in appearance to the condition seen in her oesophagus by Mr. F. A. Rose. The mucosa appeared to be uniformly thickened, and on withdrawal of the instrument fell into numerous rigid folds. No ulceration or stricture was seen.

In one case only of the series was enlargement of the spleen detected.

Response to treatment. Other observers have reported that the anaemia improved as soon as the patient was able to swallow an ordinary diet, and it has been suggested that the anaemia was solely due to the lack of food. Our experience does not agree with these observations, since, although the patients were able to eat an ordinary diet as soon as the mercury tube had been passed, the general condition and the anaemia improved very slowly. The effect of food alone was studied in the first case, but after ten weeks the

general condition was not improved and the percentage of haemoglobin had only risen to 46 per cent. Liver, 8 oz. raw and cooked, was then added to the diet and was followed by an immediate improvement in the general condition and the haemoglobin increased to 64 per cent. in four weeks. In

TABLE II
Estimations of Blood Fragility: Cases I-V

		Saline %							
		0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70
I.	22/11/29								
	Patient (Hb. 64 %)	++++	+++	++	—	—	—	—	—
	Liver 10 months								
	Control A	++++	+++	++	—	—	—	—	—
	26/5/30								
	Patient (Hb. 78 %)	++++	+++	++	—	—	—	—	—
	Control A	++++	+++	++	—	—	—	—	—
II.	22/11/29								
	Patient (Hb. 52 %)	++++	++++	++++	++	—	—	—	—
	Liver 7 months								
	Control A	++++	+++	++	—	—	—	—	—
III.	10/1/30								
	Patient (Hb. 45 %)	++++	++++	+++	++	+	—	—	—
	Control A	++++	+++	++	—	—	—	—	—
	18/1/30								
	Patient	++++	++++	+++	++	+	—	—	—
	Control A	++++	+++	+	—	—	—	—	—
	27/5/30								
	Patient (Hb. 68 %)	++++	+++	++	+	—	—	—	—
	Liver 4 months								
	Control A	++++	+++	++	—	—	—	—	—
IV.	14/1/30								
	Patient (Hb. 37 %)	++++	++++	++	+	—	—	—	—
	Control D	++++	++++	+	—	—	—	—	—
	18/1/30								
	Patient (Hb. 37 %)	++++	++++	+++	+	—	—	—	—
	Control A	++++	++++	+	—	—	—	—	—
V.	7/1/30								
	Patient (Hb. 53 %)	++++	++++	+	—	—	—	—	—
	Liver 12 months								
	Control D	++++	++	—	—	—	—	—	—
	6/2/30								
	Patient	++++	++++	++	+	—	—	—	—
	Control A	++++	+++	++	—	—	—	—	—
				less than patient					
	3/6/30								
	Patient (Hb. 40 %)	++++	++++	++	+	—	—	—	—
	Control A	++++	++	+	—	—	—	—	—

the other cases liver feeding was started as soon as the patient could swallow easily and the general condition as well as the haemoglobin percentage improved steadily. The daily amount of iron used was small, only 21 gr. of the ferri et ammonii citras. It is now recognized that ferric salts must

TABLE III.
Summary of Cases.

Patient.	Sex.	Age.	Onset of Dysphagia.	Tongue.	Corners of Mouth.	Colour of Skin.	Initial Blood Count.	Blood Count at end of Observation.	Price-Jones Curve Average Diameter.
I. S.	♀	45	5 yrs.	Sore No papillae	Sore cracked	Brownish yellow	Hb. 32 % R. 3,900,000 L. 9,000	Hb. 80 % R. 5,120,000 L. 9,200 (12.131)	6-9
II. B.	♀	39	4 yrs.	Sore No papillae	Sore cracked	Brownish yellow	Hb. 50 % R. 4,500,000 L. 5,600	Hb. 52 % R. 4,800,000 L. 6,300 (10.630)	7-05
III. Wm.	♀	38	1½ yrs.	Sore No papillae at sides	Sore cracked	Natural	Hb. 45 % R. 3,700,000 L. 14,800	Hb. 74 % R. 4,900,000 L. 8,800 (29.631)	Not estimated
IV. T.	♀	37	2 yrs.	Not sore Papillae natural	Natural	Yellowish	Hb. 37 % R. 3,700,000 L. 6,400	Hb. 59 % R. 4,840,000 L. 2,800 (22.9.30)	Not estimated
V. M.	♀	48	2½ yrs.	Sore occasionally Papillae natural	Natural	Pale	Hb. 44 % R. 4,100,000 L. 6,800	Hb. 87 % (2.5.31)	Not estimated
VI. WS.	♀	33	0	Sore 1½ yrs. No papillae at sides	Sore cracked	Brownish yellow	Hb. 45 % R. 4,800,000 L. 7,800	Hb. 100 % R. 5,520,000 L. 8,800 (4.5.31)	Not estimated

Patient.	Fractional Test Meal.	Barium Swallow.	Oesophago- scopy.	Spleen.	Other Symptoms.	Time of Observation. Months.	Liver Feeding. Months.	Fragility of Red Cells.	Van den Bergh.
I. S.	Achlorhydria	Natural	Patchy oedema	Not felt	Menorrhagia	30	16	Normal	Normal
II. B.	Achlorhydria	Natural	Mucous membrane natural	Not felt	Salpingo- oophorectomy	25	12	Increased	Not estimated
III. Wm.	Achlorhydria	Natural	Mucous membrane natural	Not felt	Menorrhagia	16	7	Increased	Normal
IV. T.	Achlorhydria	Natural	Stricture at junction of pharynx and oesophagus	Palpable	Attacks of diarrhoea	16	1½	Increased	Normal
V. M.	Achlorhydria	Delay at cardia 19/3/29 Natural 5/2/30	Mucous membrane very pale	Not felt	Mucous membrane of sigmoid very pale	26	12	Increased	Not estimated
VI. WS.	Achlorhydria	Natural	Not examined	Not felt	Miscarriage with severe haemorrhage	17	6	Increased	Normal

be given in very much larger doses in order to produce a rapid effect, and the poor results which we obtained with iron are probably due to this fact. We gave reduced iron gr. 45 in the day, together with hydrochloric acid, B.P. dr. 1, three times a day, to case V. during the second admission and the haemoglobin rose from 36 per cent. to 87 per cent. in four weeks. Davies (4) also reports a marked improvement in the anaemia in some cases after liver feeding.

Summary

The presence of increased fragility of the red cells in patients with well-marked secondary anaemia and dysphagia suggests that the anaemia is not due to the ordinary causes of secondary anaemia, and is not identical with the 'chronic microcytic anaemia' described by Witts (13). The only other condition in which increased fragility of the red cells is known is acholuric jaundice. The symptom of dysphagia has not been present in any of our cases of acholuric jaundice and is not reported nor recorded in any of the published cases. It therefore seems probable that the type of anaemia in these cases is a new and peculiar one of specific type, associated with a slight increase in the fragility of the red cells, and with achlorhydria and secondary changes in the mucous membrane of the tongue, mouth, and oesophagus, and subsequently with dysphagia. Case VI of our series suggests that the dysphagia is a late symptom of the disease. Observations on six cases form slender material on which to advance a new hypothesis, and many more cases must be investigated before it can be accepted.

A seventh patient with the typical symptoms of anaemia and dysphagia has recently been under the care of Sir Thomas Horder. She also showed an increase in the fragility of the red cells.

We have to thank Professor Fraser for permission to quote one of his cases, and Dr. Archer and Dr. Carmichael for confirming the observations on the fragility of the blood cells.

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THE SPECIFICITY OF SKIN REACTIONS IN MAN IN RELATION TO TUBERCULOUS INFECTION¹

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Introduction

THE association of tuberculin sensitivity in man with cutaneous reactivity to substances not derived from the tubercle bacillus has been studied by many workers during the last twenty years, but the results are not in agreement. The non-specific substances may be considered under two headings: (a) bacterial products not derived from the tubercle bacillus, (b) other non-specific protein substances.

(a) *Bacterial products not derived from the tubercle bacillus.* A number of the earlier writers on the specificity of the tuberculin test described skin reactions to various non-tuberculous bacterial toxins, such as derivatives of diphtheria, dysentery, cholera, typhoid, and coliform organisms, the intensity of which on the whole ran parallel with that of coincident tuberculin reactions (Entz (1908), Sorgo (1911), Rolly (1911), Tezner (1911)). These responses were usually stated to resemble tuberculin reactions in macroscopic appearance, except that they reached their height and subsided more rapidly. They were not obtained in individuals who, on account of insensitiveness to tuberculin in large doses, were believed to be tubercle-free. Sorgo reported that heated and unheated diphtheria toxin gave very similar results, and Blumenberg (1925) stated that the histology of skin reactions to tuberculin and to *B. coli* extracts was essentially the same. From their supposed close relationship with the tuberculin reaction some writers (e.g. Sorgo) have argued that the skin responses to these non-specific substances are also allergic reactions due to tuberculous infection.

Other workers, however, have expressed different views. Zieler (1911) and Zieler and Markert (1922) concluded that the skin reactions obtained with dysentery, diphtheria, and typhoid toxins, while clinically similar except for the earlier time of highest development, were fundamentally different from the true tuberculin reaction. They gave as evidence for this belief differences in histological appearance and absence of recrudescence inflammation at the sites of previous skin reactions after subcutaneous tuberculin injection. Moreover, the intensity of the reactions to these bacterial products did not run parallel with that of the tuberculin reactions in their series, and the incidence was much the same among tubercle-free and tubercle-infected individuals. A qualitative difference and lack of parallelism of intensity were also noted by Lange (1923), using diphtheria

¹ Received July 28, 1931.

and coli toxins, while Zieler and Hämel (1926) obtained strong skin reactions with *B. coli* products in tuberculin-negative cases and often none in those highly sensitive to tuberculin.

In addition to these two opposing schools there appears to be a third, which holds an intermediate view, namely, that skin reactions to non-tuberculous bacterial extracts are partly dependent upon allergy following tuberculous infection, and partly upon other factors. Thus, Hollo and Amar (1921) found the incidence of diphtheria skin reactions to be equal in tubercle-infected and tubercle-free children, but in a series of clinically tuberculous adults they noted a certain degree of parallelism between the intensity of the tuberculin and diphtheria reactions. The two responses were indistinguishable macroscopically, except for the more rapid development of the latter. Similarly, Selter (1922) and Selter and Tancré (1925) obtained inflammatory reactions with dysentery and *B. coli* products in both tubercle-free and tubercle-infected subjects, but the responses were more intense in the latter group. The stronger the allergy to tuberculin the stronger the response to non-specific products. Selter (1926) expresses the view of this school when he states that 'there is no doubt that a true tuberculin skin reaction can be elicited by non-specific substances, such as extracts from diphtheria, coli, dysentery, and prodigious bacilli. . . . A sensitiveness against the above-mentioned bacillary proteins is acquired in the human, anteceding a tuberculous infection, as was shown in infants during the first year of life. The sensitiveness increases following a tuberculous infection.'

The published work on the Schick test demonstrates that filtrates of *C. diphtheriae* have a primarily toxic effect upon the skin which is fundamentally different from true allergic reactions, and which is due to a thermolabile substance. In the light of this work it is difficult to understand the contradictory results quoted above, obtained with products of *C. diphtheriae*. It is possible that some of the reported reactions to these products correspond to the pseudo-response of the Schick test rather than to the true positive Schick reaction. The Schick pseudo-reaction has been shown to have some points of similarity to the tuberculin reaction. For instance, its incidence appears to be rare in infancy and to increase with age. According to V. Gröer and Kassowitz, however, the two reactions are quite distinct (see Medical Research Council (1923)).

The recent work on skin hypersensitiveness to various streptococcal derivatives in human subjects has a bearing on the present question, although here also the results are conflicting. Mackenzie and Hanger (1927), in a miscellaneous series of patients, were unable to establish a connexion between any particular disease or group of diseases and skin reactivity to the streptococcal derivatives used, but found that the incidence of this reactivity, like the incidence of tuberculin hypersensitiveness, was low in infancy and increased with age. Furthermore, a small group tested with tuberculin and a streptococcal filtrate, simultaneously, were stated to show parallelism between the reactions to the two substances. These authors concluded that the reactions to their streptococcal products were manifestations of acquired allergy, analogous to the tuberculin reaction, and were not due to a primarily toxic effect, analogous to the Dick and Schick reactions. But whether the streptococcal allergy was dependent upon infection by homologous or related organisms, or upon tuberculous or other unrelated forms of infection, remained undecided.

A number of subsequent observers have claimed that the incidence of skin

hypersensitiveness to certain streptococcal products is significantly higher among rheumatic individuals than among non-rheumatic controls (see Collis (1931), Coburn (1931), &c.). The reactions are of the delayed type and often resemble the tuberculin reaction closely in appearance, but differ from the latter in their incidence, for tuberculin sensitivity seems to be no more frequent among rheumatic than among non-rheumatic patients (Hart).² Coburn's findings suggest that streptococcal allergy is to some extent specific and dependent upon homologous infection.

(b) *Other non-specific protein substances.* Of these substances milk proteins and meat derivatives have received the greatest attention, but in the main with equivocal results. The published work on milk proteins has been reviewed by Tytler (1930), who states that they have given very indefinite skin reactions in the hands of most workers, and quotes Epstein (1921) who found that only the milk of tuberculin-reacting cows elicited reactions in tuberculous patients.

Reports of the association of tuberculin and peptone sensitivity are equally confusing. Thus, Tezner (1911) and Selter (1922) obtained a number of positive skin reactions with peptone solution in tuberculin-positive patients, but none in those believed to be tubercle-free, suggesting a relationship between the reactions to the two substances. On the other hand, Zieler and Markert (1922) elicited positive responses with peptone solution in tuberculin-negative as well as in tuberculin-positive cases, and failed to establish any parallelism of intensity between the two reactions.

During the last decade glycerinated veal peptone broth, of the same composition as the culture medium used in the preparation of old tuberculin, and concentrated ten times by heat, has been widely employed in the same dilution as the O.T. in order to control the tuberculin reaction. This procedure has provided an opportunity of comparing the cutaneous sensitivity to meat extracts with tuberculin sensitivity; and skin reactions to broth control solutions, qualitatively similar in macroscopic appearance to the true delayed tuberculin reaction, have been reported by a number of workers. In the majority of instances, however, these occurred in only a small proportion of tuberculin-positive reactors, the figures being 5 per cent. or less (Bass (1918), Heise and Brown (1923), Krogsgaard (1925), Tisdall and Brown (1926), Ström (1928), and Smith (1929)). Bass, Tisdall and Brown, and Smith regarded the number of persons reacting to broth controls as insignificant, while Ström and Smith suggested that the few reactions of the tuberculin type seen by them might have been due to contamination by tuberculin.

In contrast to these observations, de Potter (1926) obtained positive skin reactions with glycerinated veal peptone broth, comparable to the typical delayed response seen after tuberculin, in twelve out of twenty-eight clinically tuberculous patients, while Dölter (1926) recorded tuberculin-like responses in 100 out of 110 tuberculin-positive patients but in none of 120 negative reactors.³ Hamburger (1912) had obtained skin reactions with broth preparations when injected in large doses into tubercle-free children, but they were different in character from the typical tuberculin reaction.

² Unpublished observations on a small series of children.

³ Dölter used the Hoechst preparation of glycerinated veal broth, concentrated ten times in the usual manner. With unconcentrated broth made in this laboratory only a few reactions were obtained, and these he believed to be different in type, while negative results were obtained with other makes of broth.

It should be noted that the glycerinated veal peptone broth used for the observations quoted (except those of Hamburger and possibly Dölter) was diluted to the same extent as the tuberculin, and that the latter was used in routine doses. Hence the quantity of broth injected was relatively small, and there is no means of knowing what might have happened had larger doses been used. Another criticism is that no serious attempt has been made to determine whether all individuals giving tuberculin-like reactions to glycerinated veal peptone broth are sensitive to specific products of the growth of the tubercle bacillus as well. These results, therefore, leave unsettled the question of the incidence among the population of sensitivity to this meat extract and of its relation to tuberculous infection.

From the preceding account it is clear that the relationship between skin reactions to non-specific substances and tuberculin sensitivity, as to incidence, intensity, and character, has not been established with certainty. It is very probable that some of the conflicting reports are due to differences in the dosage employed and in the type of reaction considered. The work about to be described will be made clearer if the various types of skin response to the injection of bacterial substances are defined, so far as is possible at the present time. They differ in appearance, time of development, and significance.

1. An immediate reaction of an urticarial type, subsiding rapidly without apparent injury. This type of reaction is seen in asthmatics sensitive to epidermal proteins, and is said sometimes to follow the injection of tuberculin, streptococcal derivatives, &c.

2. An infiltrative erythematous reaction that reaches its maximum during the first twenty-four hours, and has usually disappeared by the second day. This type of reaction is most pronounced after the injection of highly concentrated solutions of old tuberculin, and may occur in tubercle-free subjects. It has been described in detail by the writer elsewhere (1932) under the heading 'atypical non-specific reactions'.

3. A delayed, persistent, inflammatory response, not reaching its maximum usually until twenty-four to forty-eight hours. This reaction is commonly an allergic manifestation. It is seen in its most typical form after the injection of tuberculin, and is then generally accepted as indicating tuberculous infection. The same type of response may also follow the injection of streptococcal derivatives, &c.

4. A primarily toxic reaction not directly connected with allergy. The Schick and Dick reactions come into this category. The response to the Schick test may resemble in appearance the allergic reactions of 3.

The present investigation is concerned with the third type of reaction only.

Present Investigation

The present communication is an account of an investigation into the skin sensitivity of clinically tuberculous and non-tuberculous human subjects to certain meat derivatives.⁴ The products used were glycerinated veal

⁴ The term positive tuberculin reaction is used throughout to indicate the third type of skin reaction (p. 52). When referring to substances other than tuberculin, the term positive reaction is limited to responses qualitatively similar in macroscopic appearance to the positive tuberculin reaction. Reactivity and sensitivity are used in the same sense.

peptone broth (referred to as G.V.B.) and its components (for formula see Appendix). The principal objects of this investigation were: (1) to determine the incidence of skin sensitivity to these non-specific substances; (2) to find its relationship to tuberculin sensitivity, and, in particular, whether it could occur in the absence of tuberculous infection; (3) to determine the constituent of meat extract that was responsible for eliciting the reaction. In contrast to previous work the G.V.B. was used in larger quantities than the old tuberculin and not primarily as a control for the latter.

Seven samples of G.V.B. were used. Six were prepared by the Wellcome Physiological Research Laboratories, viz. 1928, 9999, 1534, 1702, 1724, 1646, and one by the laboratory in Hoechst, Germany, viz. 0065. The clinical material consisted of 1,547 patients from the wards and out-patient departments of various hospitals in London and the Home Counties. About half of them were clinically non-tuberculous, and the remainder had manifest tuberculosis. Each individual was tested with one or more batches of G.V.B. and with old tuberculin (Human). The latter is referred to as O.T. It was prepared and standardized in the manner described by Okell (1930), and was found to be approximately equal in potency to the current (1928) Frankfurt standard, on which the present International Standard Tuberculin is based. The same batch (T. 1586) was used throughout. A number of patients were tested in addition with a bovine tuberculin prepared from a synthetic medium, of which the most complex nitrogenous constituent was asparagin. This tuberculin is referred to as T.S. (see Appendix).

The intracutaneous method was employed and 0.1 c.c. was injected in every case; the concentrations only are given in the tables. Reactions were read on the second, third, or fourth days. The technique is described in detail by the writer elsewhere (1932).

1. *The Incidence of Skin Sensitivity to Glycerinated Veal Peptone Broth and its Relation to Tuberculin Sensitivity*

Four samples of G.V.B. were used for this part of the investigation, viz. 1928, 9999, 1534, and 1702, and each subject was tested with one of these batches in strengths varying from 1:10,000 to 1:10, and his reaction to O.T. 1:1,000 was also ascertained. 1:1,000 is the routine standard concentration of tuberculin accepted by the majority of workers. It was adopted here, although a negative response to this dilution does not completely exclude tuberculous infection. Some of the patients were tested first with 1:10,000 O.T. for safety, and if negative to this strength were tested further with the standard concentration.

The experimental procedure and results are set out in Tables I-VI (pp. 61-63).

Eighteen patients were tested with 1928 (Table I), thirty-five with 9999 (Table II), 667 with 1534 (Table III), and 454 with 1702 (Tables IV-VI). No case is included in more than one of these tables, although where stated it may occur twice in the same table. The individuals tested

with 1702 were divided into three series (Tables IV-VI). The results of the two latter series are complicated by the arrangement of the tests made with the 1:1,000 and 1:10,000 dilutions of G.V.B. and by many of the patients having been tested with T.S. as well as with O.T. The last series (Table VI) is further complicated by allowing an interval of three days to pass between the tests made with 1:10 or 1:100 broth and the remaining injections. The reason for the complicated experimental procedure followed in these two series will be explained in a later paragraph; at present the general results are considered.

Analysing the results displayed in Tables I-VI, it will be seen that a number of positive reactors to old tuberculin gave qualitatively similar reactions to glycerinated veal peptone broth, the proportion depending on three factors: (a) the dilution of the broth preparation injected; (b) the batch of broth; and (c) the type of subject tested.

(a) The effect of varying concentrations of G.V.B. is shown in Tables V and VI. In Table V it will be seen that 22 out of 24 tuberculin-positive but clinically non-tuberculous individuals reacted to a 1:10 dilution of this sample of broth, while only 8 of them were positive to the 1:1,000 dilution. All but 1 of 48 patients with bone or joint tuberculosis were positive to the 1:10 dilution of broth, and all but 3 of 70 others to a 1:100 dilution, whereas when all these 118 bone or joint cases were tested with a 1:10,000 solution of the same broth, only 11 reacted. Again, in the same table it will be noted that 9 out of 11 phthisical patients and all of 10 cases of lupus vulgaris reacted to 1:10 broth, but only 3 of the former and 4 of the latter reacted positively to 1:1,000 and 1:10,000 dilutions, respectively. The same differences are shown in Table VI, where only 1 out of 84 patients with bone or joint tuberculosis who had reacted positively to 1:100 G.V.B. three days previously gave a positive test to a 1:10,000 dilution of the same material. Possibly, however, this finding is partly accounted for by a period of depressed reactivity following the first test.

(b) 1702 appeared to be the most active of the four batches of G.V.B., and with this sample in 1:10 concentration all but 10 of the 166 tuberculin-positive cases tested (Tables IV-VI) gave reactions indistinguishable in type from the simultaneous or subsequent tuberculin reactions. In many instances the reactions to 1:10 broth were greater than the responses to 1:1,000 or 1:10,000 old tuberculin.

The differences in skin activity of various batches of G.V.B. are shown more clearly in Part 2, where experiments involving direct comparison of two batches on the same patient are described.

(c) There was no significant difference between the percentage of reactors to the 1702 batch of G.V.B. in 1:10 dilution among those patients who were tuberculin-positive without clinical disease and among those who had clinical tuberculosis as well; and the number tested with the weaker solutions of this sample were insufficient for a comparison to be made. On the other hand, the figures of the series tested with the less active sample of G.V.B.—1534—in 1:100 and 1:1,000 dilutions (Table II) suggest that there is a difference in the degree of sensitivity of these two classes of subject to this meat extract, for the percentage of reactors among the manifestly tuberculous group was higher than among those who were tuberculin-positive without clinical disease. A corresponding difference in degree of sensitivity to tuberculin has been described by some workers (see Hart (1932)). The results obtained in this series suggest further that patients with bone or joint tuberculosis and tuberculous adenitis are more likely to

react to broth preparations than are those with pulmonary tuberculosis. Finally, comparisons, made after forty-eight hours, between the sizes of the broth and tuberculin reactions of the patients with bone or joint tuberculosis who were tested with G.V.B. 1702 in 1:100 dilution and O.T. 1:10,000, simultaneously, (Table V) showed in the main a distinct parallelism of intensity.

In contrast to the sensitivity to glycerinated veal peptone broth possessed by many of the tuberculin-positive patients in these series, only one of the 418 individuals who were negative to O.T. in the standard concentration of 1:1,000 reacted positively to G.V.B. in the strengths used, or, in other words, all but one of those who gave tuberculin-like reactions to G.V.B. gave positive reactions also to O.T. 1:1,000. The single exception, while negative to this dilution, was positive to O.T. 1:100.

Assuming that none of the more common endemic conditions are omitted from the present series, it is justifiable to infer from the data given (1) that some human subjects give tuberculin-like reactions with glycerinated veal peptone broth, and (2) that the skin sensitivity to this meat extract is confined to the tuberculin-positive members of the population, tuberculin-positive being understood here to mean positive to old tuberculin. Two questions arise from these statements. First, since old tuberculin contains G.V.B. (this being its culture medium), do some of the individuals who show skin reactivity both to untreated G.V.B. and to old tuberculin react to the latter substance not because they are sensitive to contained active products of the growth of the tubercle bacillus in the broth medium, but merely because they are sensitive to the broth medium itself? If not, a positive reaction to old tuberculin always denotes skin sensitivity to the specific products of the bacillus. Second, can the tuberculin-like reactivity to G.V.B. be explained as a sensitization phenomenon due to the simultaneous injection of old tuberculin?

(1) In order to answer the first question two methods of checking the reactions to old tuberculin were employed. The most obvious method is to control each injection of this substance by giving simultaneously an equal quantity of untreated culture medium, i.e. G.V.B., diluted to the same strength as the tuberculin, and to compare the sizes of the two reactions. If the reaction to old tuberculin is greater than that, if any, produced by the broth control, it is caused at least partly by active products of the growth of the bacillus, and not by the broth medium alone.

Where the actual batch of G.V.B. used for preparing the particular sample of old tuberculin is not available, it would seem permissible to use instead any batch of G.V.B. known to have great activity, such as 1702 of the present investigation.

On referring to the procedure of Tables V and VI it will be seen that every injection of O.T. (1:10,000 or 1:1,000) given in the 380 cases concerned was accompanied by a control injection of G.V.B. *in the same strength* as well as by the test injection of greater strength, except where the stronger solution had given a negative response less than a week before. In these

instances it was assumed that tests made with the same strength would have been negative. Thus the dilutions 1:10,000 and 1:1,000 of G.V.B. batch 1702 were used here for two purposes, first, as test substances, and second, as controls for the old tuberculin. In 295 of the 297 cases (98.3 per cent.) that gave positive reactions to O.T. it was found that the corresponding reactions to the control solutions of the same strength were either negative or, if positive, were of smaller size. The two other patients (both clinically tuberculous) gave equal reactions to old tuberculin and control. Both of them, however, were included in the group checked by the second method now to be described. (See Addendum.)

The second method of checking the reactions to old tuberculin was to give confirmatory tests using the tuberculin (T.S.) prepared from a synthetic medium of presumed negligible 'tuberculin power', a medium of much the same composition having given negative results when tested for skin activity on patients with manifest tuberculosis.

The tests for skin activity of this culture medium were made with a 1:10 dilution on 38 clinically tuberculous patients (10 lupus vulgaris, 27 bone or joint cases). No positive responses were seen, although these patients were all tuberculin-positive and reacted well to G.V.B. in a 1:10 or weaker dilution. The confirmatory tests with T.S. were made on 342 of the 380 cases composing the two series of Tables V and VI, and on 53 other cases included in a later table. (The two exceptions mentioned in the last paragraph were included in this group.) It was found that every individual who reacted to O.T. gave a typical positive reaction also to T.S., though a stronger solution was sometimes required.

Now a positive reaction to the tuberculin T.S. must be due to products of the growth of the tubercle bacillus, if the culture medium alone is incapable of eliciting a skin response. From the agreement found between the tests made with T.S. and those with old tuberculin it may, therefore, be inferred that all those giving positive reactions to the latter substance were sensitive to products of the growth of the tubercle bacillus.

(2) The second question was decided by giving a test dose of G.V.B. 1:10 or 1:100, reading the reaction at three days, and then performing the tuberculin test. This procedure was followed in 180 cases (Table VI), but the percentage positive to broth was just as large as in Table V where the broth and tuberculin were injected simultaneously. Not only were the broth reactions indistinguishable in type from the subsequent tuberculin reactions, a few even vesiculating, but in some instances they gave rise to a mild pyrexia.

This experiment is interesting in another respect for it suggests that, *given a very active sample of G.V.B. in a concentration of 1:10, it is possible with only a small error to distinguish the tuberculin-positive and negative members of the population without using tuberculin.*

Although, as shown by this experiment, the simultaneous or previous injection of tuberculin was not the cause of the tuberculin-like reactions to broth preparations, sensitization was found to be possible when the administration of tuberculin preceded the broth injection by a suitable interval.

A series of twenty-eight clinically non-tuberculous adult patients was tested with O.T. 1:10,000 or 1:1,000 and with G.V.B. 1534 1:1,000, the latter being a sample of moderate activity. Of the patients who reacted positively to the tuberculin twelve were negative to the broth. These patients received the same injections after fourteen days and their reactions were again noted. Nine of them gave larger tuberculin reactions and three about the same, and six of the former and one of the latter were now found to react to the broth. It was not decided whether the sensitization was due to the active products of the tubercle bacillus in the old tuberculin, or to a constituent of its broth medium.

The foregoing experiments enable the statements on p. 55 to be elaborated as follows: tuberculin-like reactions to glycerinated veal peptone broth are found only in individuals who are also skin-sensitive to the specific products of the growth of the tubercle bacillus, present in tuberculin whether the latter is prepared from a protein broth (as in old tuberculin) or from a synthetic protein-free medium, and the reactions to this meat extract can occur without the introduction of tuberculin into the skin elsewhere.

2. *Comparison of the 'Tuberculin Power' of Various Samples of Glycerinated Veal Peptone Broth*

In the preceding section it was stated that samples of G.V.B. differed in their tuberculin-like activity, but the evidence for this inference was obtained by testing several series of individuals each with a different batch of broth. Experiments will now be described in which the 'tuberculin power' of two samples was compared by testing the same patient with both.

The batches of G.V.B. used were 1534, 9999, 1702, 0065, 1724, and 1646. The first three have already figured in the preceding section. The procedure was to inject into the skin of the same patient equal quantities of two batches in the same dilution, together with, or followed by, old tuberculin, and to compare the number of reactors to each of the samples of broth. 0065 was compared with 1702, 1702 with 1724, 1724 with 1646, 1646 with 1534, and 1534 with 9999. The results are shown in Tables VII-IX. The same case does not occur in more than one of these tables.

The direct comparison of these batches of G.V.B. made it possible to group them in the following order of 'tuberculin power': 0065 and 1702 approximately equal strength, 1724, 1646, 1534, 9999. The great activity of 1702 indicated by the earlier experiments was thus confirmed. By comparing the sizes of the reactions to 0065 and 1702, a method avoided where possible in this investigation, it was found that the reactions to the former were either equal or larger than those produced by the latter, showing that this preparation had a slightly higher 'tuberculin power' than 1702.

No attempt was made to titrate these samples of G.V.B. against the standardized old tuberculin, although such is clearly possible in the human subject.

3. *The Component of Glycerinated Veal Peptone Broth Responsible for its 'Tuberculin Power'*

In order to discover the factors responsible for the tuberculin-like reactions elicited by G.V.B., the actual constituents of the sample 9999 were tested separately on the same patient.

The following solutions were used for this experiment :

Bacteriological peptone (P. D. & Co.) 2 per cent. in 0.5 per cent. saline, steamed till peptone dissolved, concentrated ten times. Dilutions 1 : 10, 1 : 200.*

Veal extract, i.e. veal cooked in 0.5 per cent. saline, concentrated ten times, filtered through Berkefeld candle. Dilutions 1 : 10, 1 : 200.*

Glycerin 5 per cent. in 0.5 per cent. saline, concentrated ten times, filtered through Berkefeld candle. Dilution 1 : 200*.

The whole substance, i.e. G.V.B. batch 9999 made from these components by formula given in Appendix. Concentrated ten times, filtered through Berkefeld candle. Dilutions 1 : 10, 1 : 100.*

Armour's No. 2 peptone. Dilution 1 : 10.*

* 0.5 per cent. phenol-saline was used as diluent.

A few preliminary experiments with glycerin on tuberculin-positive patients sufficed to show that this was not the responsible substance, and its use was discontinued.

Eighty-three patients (seventy-four clinically tuberculous) were tested with the whole broth 9999 in 1 : 100 dilution, with peptone 2 per cent. in 1 : 200 dilution, and with veal extract in 1 : 200 dilution; thirty other patients (all clinically tuberculous) were tested with veal extract and with peptone 2 per cent., both in 1 : 10 dilution. The results (Table X) indicate that both components, peptone and veal, are capable of eliciting the skin reaction. The activity of peptone solution by no means excludes the probability that a protein is responsible, since bacteriological peptone contains a certain amount of protein. Another series of forty patients with pulmonary tuberculosis was tested with bacteriological peptone 1 : 10 and with Armour's peptone 1 : 10, and found to be more sensitive to the former. The reactions to Armour's peptone were feeble in these patients, and the reactions to the bacteriological peptone employed were less frequent than in the bone and joint cases of series (b).

Discussion

It is generally accepted that in Europe the positive tuberculin reaction in man is only seen after tuberculous infection (see Hart (1932)). From the present experiments it may be inferred that sensitivity to certain meat derivatives is constantly associated with sensitivity to tuberculin (p. 55). Since there is no knowledge of any significant aetiological factor of non-tuberculous origin present only in tuberculin-sensitive individuals, it is,

therefore, justifiable to conclude that the meat extract reaction, like the tuberculin reaction, is diagnostic of tuberculous infection. In other words, the tuberculin reaction must be regarded as non-specific in the sense that other substances are capable of eliciting similar reactions, but specific in the sense that the response both to tuberculin and to these other substances (the meat derivatives) is probably only seen after tuberculous infection. Tuberculin is still, however, the most potent substance for eliciting skin reactions in the tubercle-infected.

The association of sensitivity to substances not derived from living bacteria with infection by a particular organism is somewhat remarkable. Although sensitivity to meat extracts would possibly be found after infection by other acid-fast bacilli, just as cross-reactions to tuberculin, johnin, &c., may occur within the acid-fast group, the association is still noteworthy. Why the distribution of sensitivity to meat extract should seem to depend upon acid-fast bacillary infection, rather than upon, say, streptococcal or *B. coli* infection, is not clear.

The experiments described in this paper afford little information as to the nature of the substances responsible for the tuberculin-like skin reactions, beyond indicating that certain peptone solutions as well as veal extract are capable of eliciting these responses in the tuberculin-sensitive. The claim made by Epstein that only the milk of tuberculin-reacting cows gave skin reactions in tuberculous patients raises the question whether a similar explanation might hold in the present instance. Dölter (1926) considered this possibility, but satisfied himself that the skin activity of the nutrient bouillon he used was not due to the meat being derived from tuberculous animals, nor to contamination during its manufacture. In the present investigation the use of seven different samples reduces the chance of the introduction of adventitious tuberculous material to a minimum, although the possibility is not completely excluded. Dölter suggests that the process of concentrating the broth solution to a tenth of its original volume may have some connexion with its subsequent activity. Further work is obviously desirable in order to decide this point.

Summary

1. Skin reactions qualitatively similar to the characteristic delayed response to tuberculin were elicited in a large number of individuals by the intracutaneous injection of glycerinated veal peptone broth (G.V.B.), such as is widely employed as a control for tuberculin tests. Quantitatively, however, more of the latter substance than of tuberculin was required to elicit the reaction.

2. The incidence of skin sensitivity to meat extract, in the form of G.V.B., was found to be practically identical with the incidence of tuberculin hypersensitiveness. Thus, nearly every individual sensitive to old tuberculin 1 : 1000 reacted to G.V.B. when a very active sample and an adequate dose

were employed (156 positive out of 166 to batch 1702 in 1:10 dilution), and all but one of over 600 individuals reacting to G.V.B. gave the characteristic response to tuberculin and were therefore presumably tubercle-infected.

3. The degree of skin sensitivity to G.V.B. of patients with manifest tuberculosis was greater than that of individuals who were tubercle-infected without clinical disease, and the sensitivity of patients with bone or joint tuberculosis was greater than that of pthisical patients.

4. The intensity of the reactions in broth-sensitive individuals was found in the main to run parallel with the intensity of the tuberculin reactions.

5. Agreement in 400 cases between tests made with old tuberculin and with a tuberculin prepared from a synthetic non-protein medium, together with the results obtained from the use of control solutions in a similar number of cases, showed that skin reactions to old tuberculin were due mainly to the products of the growth of the tubercle bacillus, and not merely to the contained broth medium.

6. Samples of G.V.B. were found to differ widely in 'tuberculin potency', though six out of the seven tested were active.

7. The property of eliciting the tuberculin-like skin reaction was found to be present both in the peptone fraction and in the veal extract fraction of G.V.B.

I am very grateful for the co-operation of the Physicians, Surgeons, and Pathologists of the hospitals from which the patients used in this investigation were drawn. These hospitals are recorded elsewhere (Hart (1932)). I wish also to make grateful acknowledgement to the following: to Dr. Bernard Schlesinger for advice on the clinical side; to Professor C. C. Okell for reading the manuscript and offering valuable criticism; to Dr. R. A. O'Brien, Director of the Wellcome Physiological Research Laboratories, for supplying the material; and to Dr. J. W. Trevan and Dr. H. J. Parish for advice on the technical side.

ADDENDUM

The G.V.B. of the present investigation had not been incubated for some weeks, as had the bacillary broth culture used for the preparation of the O.T. (see Appendix). Consequently, the possibility that the greater intensity of the reactions to O.T., as compared with those to the G.V.B. controls,—noted in the experiments described on p. 56—might have been partly due to an increased potency of the broth medium, produced by incubation, was not excluded.

TABLE I.* *G.V.B. 1928*

18 cases tested with G.V.B. 1:1,000 and O.T. 1:1,000.

G.V.B.	Negative to O.T. 1:1,000.	Positive to O.T. 1:1,000.	
		Clinically Non-T.B.	Clinically Tuberculous.
Tested with 1:1,000	5	5	8
Positive†	0	0	0

* The same case is not included in more than one of the tables, although where indicated it may occur twice in the same table.

† Here and elsewhere in the tables 'positive' has the meaning given in footnote, p. 52.

TABLE II. *G.V.B. 9999*

35 cases tested with G.V.B. 1:100 and O.T. 1:1,000.

G.V.B.	Negative to O.T. 1:1,000.	Positive to O.T. 1:1,000.		Type of Clinical T.B. that Re- acted to G.V.B.
		Clinically Non-T.B.	Clinically Tuberculous.	
Tested with 1:100	16	12	7	
Positive	0	2	4	3 out of 6 bone or joint

TABLE III. *G.V.B. 1534*

667 cases:

(a) 423 cases tested with G.V.B. 1:100 and O.T. 1:1,000.

(b) 244 different cases tested with G.V.B. 1:1,000 and O.T. 1:1,000.

G.V.B.	Negative to O.T. 1:1,000.	Positive to O.T. 1:1,000.		Type of Clinical T.B. that Re- acted to G.V.B.
		Clinically Non-T.B.	Clinically Tuberculous.	
(a) Tested with 1:100	186	94	143	
Positive	0	14	40	20 out of 109 pul- monary 7 out of 14 bone or joint 7 out of 8 adenitis
(b) Tested with 1:1,000	94	95	55	
Positive	0	9	19	4 out of 19 pul- monary 4 out of 6 bone or joint 4 out of 8 adenitis 4 out of 6 lupus

TABLE IV. *G.V.B. 1702*

74 cases :

(a) 74 cases tested with *G.V.B.* 1 : 10 and *O.T.* 1 : 1,000.(b) 29 of these cases also tested with *G.V.B.* 1 : 100 simultaneously.

<i>G.V.B.</i>	Negative to <i>O.T.</i> 1:1,000.	Positive to <i>O.T.</i> 1:1,000.		Type of Clinical T.B.
		Clinically Non-T.B.	Clinically Tuberculous.	
(a) Tested with 1:10	34	17	23	Various
Positive	1*	17	22	
(b) Tested with 1:100	18	9	2	
Positive	0	7	2	

* This case, negative to *O.T.* 1:1,000, was, however, positive to *O.T.* 1:100.TABLE V. *G.V.B. 1702*

200 cases :

(a) 113 cases tested with *G.V.B.* 1 : 10 together with either (i) *O.T.* 1 : 1,000 and *G.V.B.* 1 : 1,000, or (ii) *O.T.* 1 : 10,000 and *G.V.B.* 1 : 10,000, followed in less than a week by *O.T.* 1 : 1,000 and *G.V.B.* 1:1,000 if negative to *O.T.* 1:10,000. (*G.V.B.* 1 : 1,000 omitted from (ii) if already negative to 1 : 10 dilution.)

(b) 87 different cases tested with *G.V.B.* 1 : 100 together with *O.T.* 1 : 10,000 and *G.V.B.* 1 : 10,000, followed in less than a week by *O.T.* 1 : 1,000 and *G.V.B.* 1 : 1,000 if negative to *O.T.* 1 : 10,000. (*G.V.B.* 1 : 1,000 omitted if already negative to 1 : 100 dilution.)

(c) Results of the 61 cases of (a) that were tested in first instance with *G.V.B.* 1 : 1,000.

(d) Results of the 52 cases of (a) and the 87 cases of (b) that were tested in first instance with *G.V.B.* 1 : 10,000.

<i>G.V.B.</i>	Negative to <i>O.T.</i> 1:1,000.	Positive to <i>O.T.</i> 1:1,000.		Type of Clinical T.B. that Re- acted to <i>G.V.B.</i>
		Clinically Non-T.B.	Clinically Tuberculous.	
(a) Tested with 1:10	26	24	63	47 out of 48 bone or joint 9 out of 11 pul- monary
Positive	0	22	60	
(b) Tested with 1:100	3	—	84	67 out of 70 bone or joint 10 out of 10 lupus
Positive	0*	—	81†	
(c) Tested with 1:1,000	24	24	13	3 out of 11 pul- monary
Positive	0	8	5	
(d) Tested with 1:10,000	5	—	134	4 out of 10 lupus 11 out of 118 bone or joint
Positive	0	—	16	

* These were negative also to *G.V.B.* 1:10.† The three cases negative to *G.V.B.* 1:100 were positive to 1:10 dilution.

175 of the 200 cases received confirmatory tests with tuberculin T.S. 1 : 10,000, 1 : 1,000, or 1 : 100. Cases that were positive to *O.T.* 1 : 1,000 but negative to T.S. 1 : 10,000 or 1 : 1,000 were tested with T.S. 1 : 100. All cases positive to *O.T.* 1 : 1,000 were found to be positive to T.S. in one of these strengths. These tests with T.S. were carried out at the same time as those made with *O.T.*

180 cases:

TABLE VI. *G.V.B. 1702*

(a) 84 cases tested with G.V.B. 1:10 alone, and three days later, when result seen, with O.T. 1:1,000 and G.V.B. 1:1,000. (G.V.B. 1:1,000 omitted if already negative to 1:10 dilution.)

(b) 96 different cases tested with G.V.B. 1:100 alone, and three days later, when result seen, with O.T. 1:10,000 and G.V.B. 1:10,000, followed in less than a week by O.T. 1:1,000 and G.V.B. 1:1,000 if negative to O.T. 1:10,000. (G.V.B. 1:10,000 and 1:1,000 omitted if already negative to 1:100 dilution.)

(c) Results of the 35 cases of (a) that, positive to G.V.B. 1:10, were tested with G.V.B. 1:1,000 at three days.

(d) Results of the 84 cases of (b) that, positive to G.V.B. 1:100, were tested with G.V.B. 1:10,000 at three days.

G.V.B.	Negative to O.T. 1:1,000.	Positive to O.T. 1:1,000.		Type of Clinical T.B.
		Clinically Non-T.B.	Clinically Tuberculous	
(a) Tested with 1:10	45	33	6	
Positive	0	30	5	
(b) Tested with 1:100	9	—	87	All bone or joint
Positive	0*	—	84†	
(c) Positive to 1:10, tested with 1:1,000	—	30	5	
Positive	—	8	0	
(d) Positive to 1:100, tested with 1:10,000	—	—	84	All bone or joint
Positive	—	—	1	

* These were negative also to G.V.B. 1:10.

† The three cases negative to G.V.B. 1:100 were positive to 1:10 dilution.

167 of the 180 cases received confirmatory tests with tuberculin T.S.; the procedure and results were as described in Table V. The tests were carried out at the same time as those made with O.T.

54 cases:

TABLE VII. *G.V.B. 0065 and 1702*

(a) 9 cases tested with G.V.B. batches 0065 and 1702 in 1:10 dilution, followed two to four days later, when results seen, by O.T. 1:1,000.

(b) 45 different cases tested with G.V.B. batches 0065 and 1702 in 1:100 dilution, together with O.T. 1:10,000, followed in less than a week by O.T. 1:1,000 if negative to O.T. 1:10,000.

G.V.B.	Positive to O.T. 1:1,000.		Type of Clinical T.B.
	Clinically Non-T.B.	Clinically Tuberculous.	
(a) Tested with 0065 and 1702 in 1:10 dilution	9	—	
Positive to both	7	—	
Positive to 0065, negative to 1702	1	—	
Positive to 1702, negative to 0065	0	—	
(b) Tested with 0065 and 1702 in 1:100 dilution	—	45	43 bone or joint
Positive to both	—	44	
Negative to both	—	—	

53 of the 54 cases received confirmatory tests with T.S.; the procedure and results were as described in Table V. The tests were carried out at the same time as those made with O.T.

TABLE VIII. *G.V.B. 1702 and 1724*

49 cases:

(a) 10 cases tested with G.V.B. batches 1702 and 1724 in 1:10 dilution, together with O.T. 1:1,000.

(b) 32 different cases tested with G.V.B. batches 1702 and 1724 in 1:10 dilution, followed three days later, when results seen, by O.T. 1:1,000.

(c) 7 different cases tested with G.V.B. batches 1702 and 1724 in 1:100 dilution, together with O.T. 1:1,000.

G.V.B.	Negative to O.T. 1:1,000.	Positive to O.T. 1:1,000.		Type of Clinical T.B.
		Clinically Non-T.B.	Clinically Tuberculous.	
(a) and (b) Tested with 1702 and 1724 in 1:10 dilution	12	15	15	Various
Positive to both	0	4	7	
Positive to 1702, negative to 1724	1*	10	7	
Positive to 1724, negative to 1702	0	0	0	
(c) Tested with 1702 and 1724 in 1:100 dilu- tion	—	—	7	Bone or joint
Positive to both	—	—	7	

* This case, negative to O.T. 1:1,000, gave a doubtful feeble positive reaction to O.T. 1:100.

TABLE IX. *G.V.B. 1724, 1646, 1534, 9999*

109 cases:

(a) 49 cases tested with G.V.B. batches 1724 and 1646 in 1:10 dilution, together with O.T. 1:1,000.

(b) 7 different cases tested with G.V.B. batches 1646 and 1534 in 1:1,000 dilution, together with O.T. 1:1,000.

(c) 30 different cases tested with G.V.B. batches 1534 and 9999 in 1:100 dilution, together with O.T. 1:1,000.

(d) 23 different cases tested with G.V.B. batches 1534 and 9999 in 1:1,000 dilution, together with O.T. 1:1,000.

G.V.B.	Positive to O.T. 1:1,000, Clinically Tuberculous.	Type of Clinical T.B.
(a) Tested with 1724 and 1646 in 1:10 dilution	49	All pulmonary
Positive to both	16	
Positive to 1724, negative to 1646	14	
Positive to 1646, negative to 1724	0	
(b) Tested with 1646 and 1534 in 1:1,000 dilution	7	Various
Positive to both	0	
Positive to 1646, negative to 1534	3	
Positive to 1534, negative to 1646	0	
(c) Tested with 1534 and 9999 in 1:100 dilution	30	{ 15 pulmonary 15 bone or joint
Positive to both	9	
Positive to 1534, negative to 9999	10	
Positive to 9999, negative to 1534	0	
(d) Tested with 1534 and 9999 in 1:1,000 dilution	23	18 bone or joint
Positive to both	11	
Positive to 1534, negative to 9999	11	
Positive to 9999, negative to 1534	0	

TABLE X. *G.V.B. 9999 and its Constituents, and Armour's Peptone No. 2. (See Appendix)*

161 cases:

- (a) 83 cases tested with G.V.B. batch 9999 in 1:100 dilution and bacteriological peptone and veal extract in 1:200 dilution, together with O.T. 1:1,000.
 (b) 38 different cases tested with veal extract and bacteriological peptone in 1:10 dilution, together with O.T. 1:10,000, followed in less than a week by O.T. 1:1,000 if negative to O.T. 1:10,000.
 (c) 40 different cases tested with bacteriological peptone and Armour's peptone No. 2 in 1:10 dilution, together with O.T. 1:1,000.

Non-specific substance.	Negative to O.T. 1:1,000.	Positive to O.T. 1:1,000, Clinically T.B.	Type of Clinical T.B.
(a) Tested with G.V.B. 1:100, peptone and veal ex- tract 1:200	9	74	(51 bone or joint 13 pulmonary)
Positive to all	0	33	
Positive to veal and pep- tone only	0	13	
Positive to veal only	0	3	
Positive to peptone only	0	1	
Positive to G.V.B. and veal only	0	5	
Positive to G.V.B. and peptone only	0	0	
Positive to G.V.B. only	0	1	
(b) Tested with peptone and veal extract in 1:10 dilution	—	38	34 bone or joint
Positive to both	—	35	
Positive to veal, negative to peptone	—	1	
Positive to peptone, nega- tive to veal	—	0	
(c) Tested with bacterio- logical peptone and Armour's No. 2 peptone in 1:10 dilution	—	40	All pulmonary
Positive to both	—	5	
Positive to bacteriological peptone, negative to Armour's peptone	—	14	
Reverse	—	0	

APPENDIX

Preparation of the Glycerinated Veal Peptone Broth (G.V.B.) used in this Investigation

Veal extract, i.e. veal cooked in 0.5 per cent. saline.

Bacteriological peptone added to make 2 per cent. (The bacteriological peptone was obtained by peptic digestion of a protein of animal origin. Average total nitrogen 14 per cent., and ash content about 2 per cent.)

Glycerin added to make 5 per cent.

Filtered through Berkefeld candle.

Concentrated ten times by heat.

Diluted to required strength with 0.5 per cent. phenol-saline before use.

Note.—The same formula was used for the culture medium for preparing the old tuberculin, but the tuberculin formed after six weeks' incubation of the bacillary broth culture, and not the untreated broth, was concentrated ten times.

Composition of the Synthetic Culture Medium used for the Tuberculin T.S.

Sodium phosphate	3 gm.
Potassium phosphate	4 gm.
Magnesium sulphate	0.6 gm.
Magnesium citrate	2.5 gm.
Asparagin	5 gm.
Glycerin	20 c.c.
Distilled water to 1 litre.	
Neutralized with 10 per cent. sodium carbonate. Boiled. Filtered.	

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A STUDY OF THE SLEEPING PULSE-RATE IN RHEUMATIC CHILDREN¹

By BERNARD SCHLESINGER

(From the Children's Heart Hospital, West Wickham)

To speak of cure in the rheumatism of childhood is always a little unsafe, for the disease may only be in a dormant stage and still liable to relapse into activity. In favourable cases it is wiser, therefore, as in tuberculosis, to talk of an arrest of the process. This applies particularly to children with rheumatic heart affections, and many tests have been devised to ascertain whether the disease is active or quiescent. From the clinical standpoint, the continuous absence of temperature, a regular normal pulse-rate, a steady gain in weight, and no advance in the cardiac signs are most important evidence of an arrest of the disease. Complete reliance cannot, however, be placed on these criteria, and their converse does not always indicate the presence of active rheumatism. Slight pyrexia in childhood may so easily have causes other than rheumatism, whilst on the other hand the most active rheumatism may be present without fever. Tachycardia is one of the main accompaniments of carditis, but, as will be emphasized later, rapid pulse-rate may equally well be of nervous origin and lead to the mistaken diagnosis of serious heart disease. A regular rise in weight in a child is generally a favourable sign; it can certainly occur at times with advancing heart disease, but in cases of arrested endocarditis other causes, in particular chronic tonsillar sepsis, may prevent a gain.

Diminution or, at most, constancy of the physical signs in the heart would seem to be essential before excluding a smouldering valvular inflammation, but the scarring may well occur during the process of healing, and it is at this stage that the murmurs become increasingly audible. At any rate, the small vegetations and associated myocarditis during the earliest and most active part of the disease may produce no audible changes in the heart-sounds.

Pathologists have tried where clinicians have failed, and several blood tests have been employed by them to diagnose an active rheumatic state. A white cell count and the sedimentation rate are the best known. Thus, Swift and Miller (1) look upon leucocytosis as an index of activity, but Perry (2) is not so impressed with the reliability of this test. The sedimentation rate has been extensively studied by Kahlmeter (3) who regards it as valuable evidence of active rheumatic disease; on the other hand,

¹ Received July 22, 1931.

Peterman and Seegar (4) are not so enthusiastic over the test and regard it as unreliable. In many cases the rheumatic child looks obviously so ill that there is no hesitation in pronouncing the infection still present, but in others we are left in doubt whether or not to advise further rest and treatment.

To allow a child to run about and lead an ordinary life with an active carditis present is courting disaster. It is almost as harmful to render a child an introspective invalid by keeping it recumbent for months on end because of a moderate persistent tachycardia which is really nervous in origin.

An increasing tendency towards this mistaken treatment has prompted the present investigation, particularly as certain rheumatic heart clinics have adopted a complicated system of cardiac efficiency tests, based principally on changes in the pulse-rate reaction to posture and exercise. These may exclude the presence of active carditis, but the converse does not necessarily follow, since many uncontrollable factors other than rheumatic heart disease may prevent a highly strung child conforming to the normal pulse-rate figures. If, on the other hand, some standard in the range of pulse-rate could be established in the absence of the nervous factor—during sleep—it might prove to be an additional help in the diagnosis of active heart disease.

The study has been carried out during the last three years at the West Wickham Heart Hospital, where there is splendid opportunity of keeping children who are recovering from recent rheumatic heart disease under continuous observation for many months at a time.

It soon became apparent that many of the children showed a pulse-rate when examined by the visiting doctor out of all proportion to that noted and charted regularly by the accustomed nurse. Even the advent of a nurse strange to the child was often found sufficient to raise the rate above its usual level. How much more unreliable, then, must be the estimation of the normal pulse-rate amidst the excitement of an out-patient clinic!

Many influences bear on the frequency of the heart-beat. With a normal rhythm the sino-auricular node is the pacemaker, and this in turn is controlled by impulses conveyed by the vagus and sympathetic nerves, which are antagonistic in their action. Even at rest the minor activities and excitement of consciousness are sufficient to act on the sympathetic nerve, with the result that the day or 'alert' pulse is more rapid than that during sleep. It is only under such states of subconsciousness that the vago-sympathetic balance is strictly undisturbed. Diminished metabolism and slightly-lowered temperature are also factors which bring about reduction of the pulse-rate during sleep, but they are more or less constant and have therefore been disregarded in the present investigation.

Pyrexia has a considerable bearing and, for this reason, patients who have shown any degree of fever have been excluded.

Method of Estimation

The most accurate method is the mechanical registration by an instrument such as the cardi tachometer described by Boas and Weiss (5). This can be strapped to the patient and he is permitted to move about the room within limits. Meanwhile a continuous record of the cardiac rate is registered on

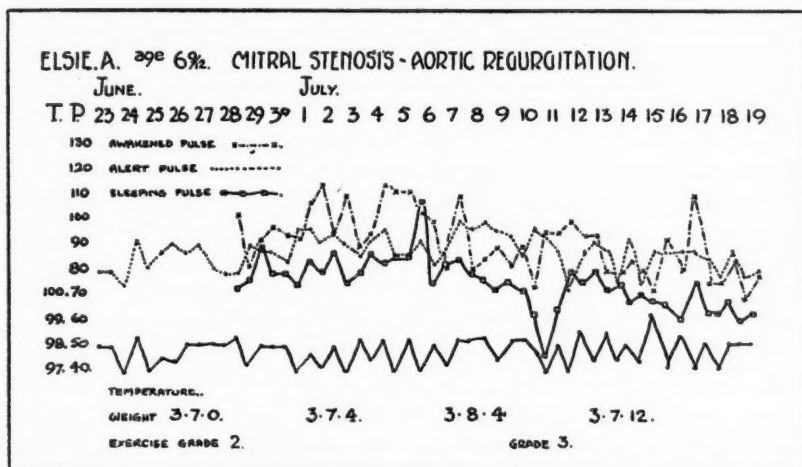


CHART 1. Showing effect of rousing the patient from sleep before taking the pulse, and the abnormally high figures obtained. In order to estimate the accurate sleeping rate great care must be taken not to disturb the patient.

a drum, and variations of the speed can be accurately noted with the patient asleep or during his various activities awake. Not having such an instrument at our disposal, and since the observations were to extend to several hundred cases, the ordinary method of pulse taking was adopted. By day, with the patient awake and the same set of nurses in charge, this presented no difficulty and was reasonably accurate, but during sleep serious fallacies could readily occur. Thus the pulse-rate in healthy children was found to show a fairly constant drop during sleep, but if the patient were disturbed and half awakened while the pulse was being taken, this was sufficient to send the rate to a level even higher than that recorded during the waking hours of the day.

Several cases were purposely awakened at night after the sleeping pulse had first been noted in order to demonstrate this point, and the accompanying chart (Chart 1) is a good example. Due care must therefore be exercised not to disturb the child, and, should this happen, the rate should not be recorded on that occasion.

In a very short time it was found that the nurses acquired the necessary touch, and after the first few nights most of the children slept on peacefully. It was found best to take the pulse at the wrist by quietly slipping the hand under the bed-clothes. The face being more sensitive, the temporal pulse

could not be used for fear of waking the patient. Some children have a habit of sleeping with both arms under them, and in that event the only possible method was to pull one arm out over the bed-clothes and wait until the child was asleep once more before taking the pulse.

Normal Variation in Heart-rate during Health

Sutherland and McMichael (6) have pointed out that the diurnal variation between the pulse-rate in the afternoon and in the early morning during sleep was on an average 34 beats per minute. This they attributed to nervous influences, and found it to be most pronounced in rheumatic children with a nervous and excitable temperament.

In the present investigation, however, the alert pulse was found to show such variations, particularly in the evenings, that by itself it could not be taken as a reliable index of the average rate during the waking hours. In fact, in order to compare the speed of the pulse during sleep and awake, due regard must be paid to the morning and evening variation that occurs normally in health. This is greatest during the waking hours, as, for instance, 6 a.m. and 6 p.m., but is also seen in a lesser degree at night during sleep at 10 p.m. and 2 a.m., the regular times at which observations on the pulse were made in this investigation. In order, therefore, to ascertain the average alert pulse-rate during the day, the mean of the highest and lowest rates recorded over a period of one, two, or more weeks must be taken. The same applies to the calculation of the average sleeping pulse-rate. By this method the variation will be much less than Sutherland and McMichael's figures, 34, and will be more in the region of 10 beats per minute.

Before studying the effect of pathological conditions such as active rheumatic heart disease on the variation of the pulse-rate, the physiological range was first calculated in over a hundred healthy children arranged into groups up to 15 years of age. They were carefully chosen over a period of two years from convalescent cases who had been admitted to the children's ward of the Royal Northern Hospital with various complaints. Great care was taken to see that they had quite recovered from their illness. No case showing any sign of fever was chosen, and in most instances a steady gain in weight was additional evidence of their return to health.

TABLE I. *Comparing the Average Normal Pulse-rate awake and asleep in 106 healthy children arranged into Age Groups*

Age.	No. of Cases.	Alert Pulse.	Sleeping Pulse.	Difference.
0-3 months	11	132	128	4
3-6 months	6	123	119	4
6-12 months	5	120	113	7
1-2 years	7	107	99	8
2-5 years	17	92	84	8
5-10 years	46	85	77	8
10-15 years	14	85	75	10

It will be seen (Table I) that during infancy the difference between the alert and sleeping pulse-rate is not so marked, but that gradually as the child grows older it becomes greater, reaching 10 per minute at the age of 10 to 15 years. This is what might be expected, since external affairs have not the same effect during the first six months of life as later, when the nervous system is rapidly becoming more fully developed.

Variation of the Pulse-Rate in Rheumatic Heart Disease

The study was next extended to a large group of children with rheumatic heart disease. The majority had *quiescent* lesions so far as could be judged from their general clinical behaviour, their steady gain in weight and normal or subnormal temperature, these criteria, as already stated, being accepted with due reservation.

TABLE II. *Showing the Average Pulse-rate in 131 quiescent cases of Rheumatic Heart Disease, compared to that of rheumatic patients without carditis, and that of normal healthy children*

Pulse.	Average Pulse-rate.					
	5-10 years.			10-15 years.		
	Alert.	Sleeping.	Difference.	Alert.	Sleeping.	Difference.
Rheumatic heart disease. Quiescent. (131 cases)	88	78	10	84	75	9
Myocarditis	88	78	10	82	75	9
Mitral regurgitation	87	77	10	84	74	10
Mitral stenosis	89	78	11	85	75	10
Mitral and aortic disease	87	79	8	85	76	9
Rheumatism without carditis	89	78	11	83	74	9
Normal health	85	77	8	85	75	10

The type of cardiac lesion present appears to have little effect on the pulse-rate.

Many of the children on whom these investigations were carried out were still entirely in bed. When they had been up for varying periods during the day, an hour at least was allowed to elapse after their return to bed before a record of the evening alert pulse was taken. In this way any possible tachycardia due to exercise was excluded.

Dividing them up into two age groups, 5-10 years and 10-15 years (Table II), it will be apparent that the variation in pulse-rate is practically identical with that of the first group of healthy children. The character of the lesions, in every case without cardiac failure, will also be noticed to have no appreciable effect on the normal drop in rate during sleep.

The next group examined were those who showed obvious *active* carditis, either by a rapid increase in the size of the heart whilst under observation, by preceding pericarditis, or the development of subcutaneous nodules. In two cases the pathological changes found at autopsy afforded additional

proof of active cardiac rheumatism. Readings were only taken into account after any pyrexia had subsided, so that in this respect the group conformed to the previous ones and fair comparison could be made. It will at once be seen (Table III) that with active carditis present, besides the expected

TABLE III. *Comparing the effect of quiescent and active carditis on the Pulse-Rate. Tachycardia of both the sleeping and alert pulse occurs when the condition is active, but that during sleep to a relatively greater extent, so that the normal difference is reduced by half*

Age Group.	Pulse-rate.						
	5-10 years.			10-15 years.			
	Pulse.	Alert.	Sleeping.	Difference.	Alert.	Sleeping.	Difference.
Quiescent		88	78	10	84	75	9
Active carditis (35 cases)		110	104	6	111	107	4

tachycardia during the waking hours, the accustomed drop during sleep was diminished to about half the normal, and was on an average in the region of 5 instead of 10 beats per minute. Many cases in fact showed no difference whatever between the alert and sleeping pulse-rates. Fourteen patients were observed both during the quiescent and active stages of the disease, and in nearly every case the thesis is borne out that tachycardia is present both day and night with active carditis, and the alert and sleeping pulse-rates approximate each other (Table IV).

TABLE IV. *A Comparison of the Alert and Sleeping Pulse-Rates during active and quiescent phases of the disease in each case*

Pulse.	Rheumatism Quiescent.			Active Carditis.			Type of Activity.
	Alert.	Sleeping.	Difference.	Alert.	Sleeping.	Difference.	
K. C.	91	82	9	100	96	4	Carditis. Nodules
M. N.	86	76	10	110	105	5	Carditis. Nodules
E. R.	96	81	15	94	90	4	Carditis
I. R.	90	70	20	118	112	6	Carditis. Arthritis
P. B.	98	87	11	110	105	5	Carditis. Nodules.
J. T.	90	74	16	88	84	4	Chorea Endocarditis.
D. D.	84	80	4	118	116	2	Chorea Carditis. Failure.
M. D.	89	83	6	107	105	2	Nodules
D. Fr.	84	79	5	112	104	8	Carditis. Nodules
D. Frs.	88	78	10	107	102	5	Carditis
H. H.	90	80	10	104	101	3	Pericarditis. Failure
C. M.	78	68	10	106	106	0	Carditis. Nodules.
J. M.	88	78	10	102	94	8	Chorea Nodules
A. P.	107	94	13	120	112	8	Pericarditis. Nodule
							Carditis

Opportunity arose of checking this both ways. Chart 2 shows a comparison of the pulse chart of a quiescent case of mitral stenosis in July 1928

and later on her return to hospital with a relapse of active carditis, pericarditis, and subcutaneous nodules for the first time in May 1929. Chart 3 shows the converse, a case with active carditis in January 1930, becoming quiescent in July of the same year and having remained so up to date. In each instance the variation and approximation of the two pulse-rates are seen to coincide with the healthy and sick periods respectively.

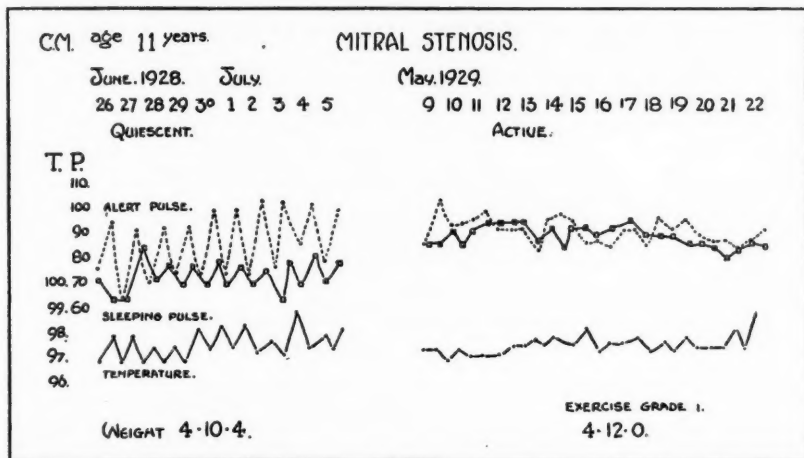


CHART 2. A comparison of the alert and sleeping pulse-rates in a child at different stages of her rheumatic infection.

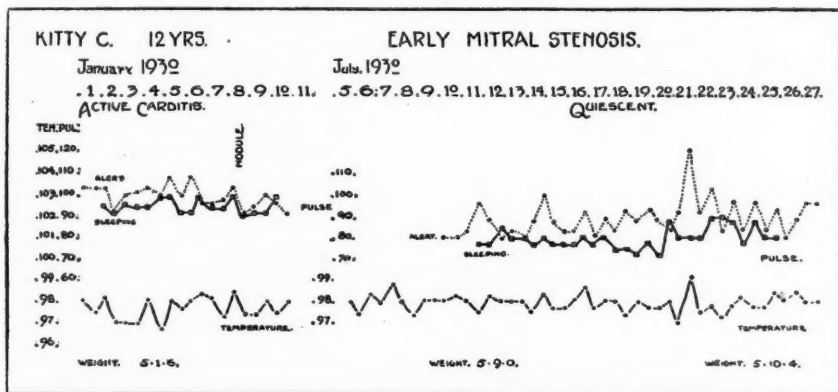


CHART 3. A comparison of the alert and sleeping pulse-rates in a child at different stages of her rheumatic infection.

The Clinical Value of Sleeping Pulse-Rate Estimation

Estimation of the sleeping pulse-rate is chiefly valuable in excluding nervous tachycardia. Thus, for instance, Chart 4 shows the case of a girl aged $6\frac{1}{2}$ years who had been kept strictly in bed for six months on account

of a slight pyrexia in the region of 99° F. and a pulse-rate of 90 to 110, supposedly due to rheumatism. The sleeping pulse-rate when taken, however, was normal and 22 beats per minute below the alert pulse. There

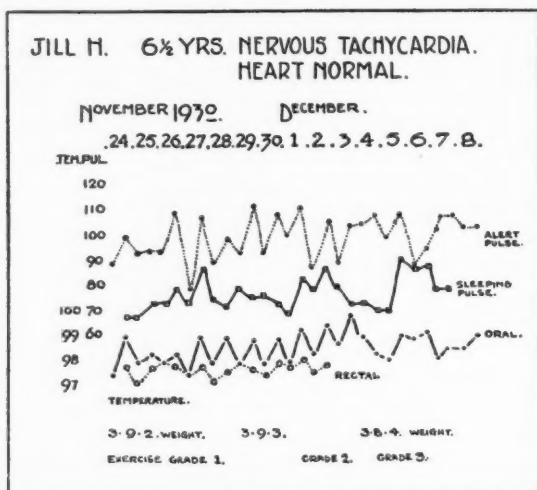


CHART 4. Demonstrating the value of sleeping pulse-rate estimations in the diagnosis of nervous tachycardia. A curious feature of this case was a lower rectal than oral temperature.

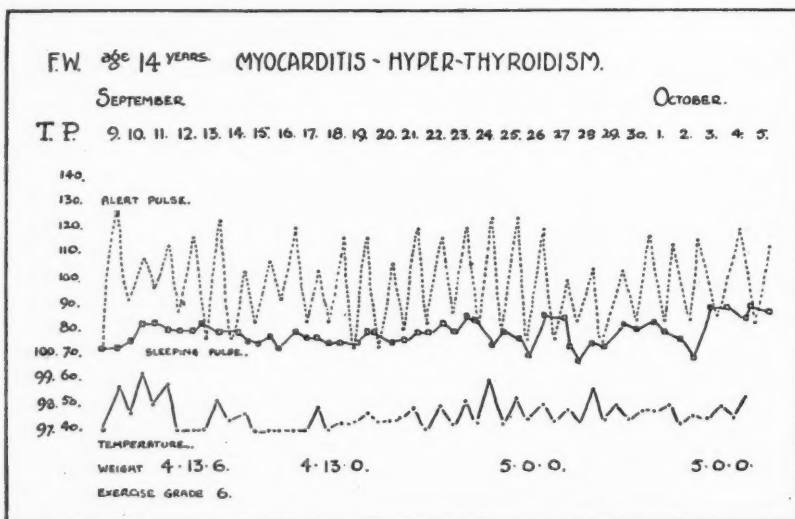


CHART 5. Tachycardia of nervous origin associated with slight over-action of the thyroid gland with approaching puberty. The sleeping pulse-rate shows no increase above the normal.

being no evidence of cardiac disease, she was allowed to get up and lead a normal life and has kept quite well since.

Chart 5 is a similar case, only here the child had had definite rheumatism

with slight cardiac involvement. This cleared up entirely, and the tachycardia by day for which the child had been invalided in bed was thought to be merely due to slight over-action of the thyroid at the commencement of puberty. The sleeping pulse being well below the alert pulse (20 beats per minute), the girl was allowed to get up and run about, with satisfactory results.

In a case of post-scarlatinal rheumatism with mitral endocarditis which was transferred to West Wickham on account of tachycardia, the relatively lower and normal sleeping pulse-rate (Chart 6) led us to believe that the tachycardia was not due to active carditis. The child was allowed to resume a normal life, and, when seen two years later, had remained in good health and showed no advance of heart disease.

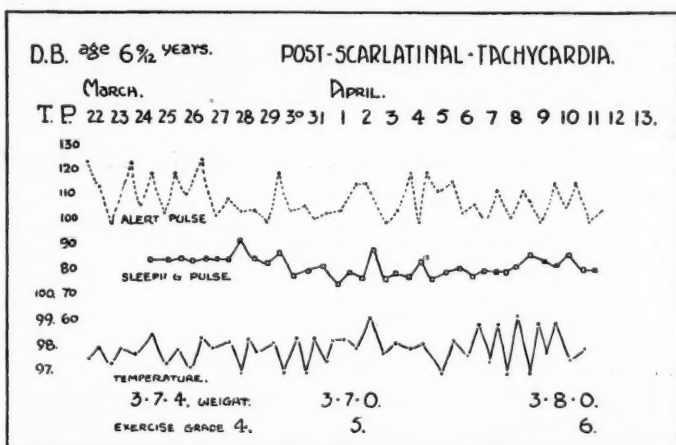


CHART 6. The low normal sleeping pulse-rate in this case led to the abandonment of cautious measures. The child was allowed to get up and progressed well.

Hutchison (7) has shown that a gradually increasing tachycardia by day, even in the absence of fever, is a strong indication of renewed carditis. Unfortunately we are not always able to witness this rise in the pulse-rate at the time and are only confronted with the case with the tachycardia present. It is in such instances that a study of the sleeping pulse-rate is of immense value.

The investigations reported here have demonstrated conclusively that with obvious active carditis the sleeping pulse-rate is raised. The converse is therefore probably also true, namely, that the discovery of a sleeping tachycardia in a doubtful case may be taken as strong evidence of rheumatic activity. This is no presumption after what has been said in regard to the pulse in nervous tachycardia.

Having accepted this as a correct interpretation, it is disconcerting to find a normal sleeping pulse-rate in a small proportion of rheumatic cases with

subcutaneous nodules present. This at first was held to be a serious argument against the correctness of the theory until those few cases had been watched over several years and no advance in the old cardiac lesion detected. To regard subcutaneous nodules as an outward indication of a similar pathological process in the myocardium is generally the safest plan and the one, at any rate, adopted by the author. It may be necessary to modify one's views and to accept the possibility of the rheumatic process in certain rare cases becoming arrested in the heart in advance of other tissues in the body.

Some years ago Miller (8) brought forward this argument, and the present study does support his theory to a certain extent.

Perhaps the most graphic result of this raising of the sleeping pulse-rate during active carditis on the charts and tables shown here is the diminution in the gap between the alert and sleeping pulse levels. This is true in most cases, and a glance at the chart will often show at once the state of the rheumatic infection. Unfortunately there are exceptions, and some children with active heart disease will still show the gap on their charts, although at a higher level. The probable explanation is a superimposed nervous element when awake.

Some modification in our statement is thus required and the following will include every type of case.

Conclusions

1. Study of the pulse-rate, awake (the alert pulse), is not sufficient to establish the presence of active carditis in afebrile children with rheumatic heart disease.
2. Normally the sleeping pulse-rate is on an average 10 beats per minute slower than the alert pulse.
3. A rapid alert pulse-rate unaccompanied by a similar increase in the rate during sleep points to a nervous tachycardia.
4. Active carditis can be presumed if, in the absence of fever, the sleeping pulse-rate approximates the alert rate so as to diminish or abolish the normal variation between the two. A sleeping pulse-rate continuously and decisively above the normal is also strong evidence of active heart disease, even though the variation between the rates during sleep and awake persists.

As stated, this study of the pulse-rate has been confined to normal convalescent children and those with rheumatic heart disease. The findings are not claimed as specific to this complaint, and it is quite possible that the same rules pertain to other active infections in children.

My thanks are due to the nursing staff of the West Wickham Heart Hospital for their kind co-operation in this investigation and in particular

to Sister Rye, who during the last three years on night duty has shouldered the greatest burden of the work. I am also grateful to Sister Bennetts at the Royal Northern Hospital who supervised the pulse taking and charting in my ward over the same period.

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EPIDEMIC ACUTE RHEUMATISM IN A PUBLIC SCHOOL¹

By W. H. BRADLEY

It is almost traditional that rheumatic fever is rare in Public Schools. Miller (1) reports the 'complete absence of acute rheumatism' in these institutions, and argues in favour of tonsillectomy (2) which has been performed in the majority of public school boys before they go to school. The disease is not common in large schools, but Glover (3) records two small epidemics, and both Haig-Brown (4) and Raven (5) were public school doctors. I am informed that, apart from the events described in this paper, two other English schools have suffered from waves of rheumatism since the beginning of 1930.

The school at present under consideration is healthily situated and housed in good buildings. A resident medical officer is employed and hygienic arrangements are satisfactory, except for some overcrowding and the fact that the boys live in one building and not in separate houses. The junior school (boys 9-14 years) is, as far as practicable, segregated from the upper school (14-18 years). The late medical officer remembers no case of acute rheumatism in forty years work at the school, and there is little doubt that an interval of forty-five years preceded the present appearance of this disease in the school in May 1929 when schoolboy No. 57, a female shoe-cleaner, and a male villager had acute rheumatism. Chorea followed in two other female villagers at the end of July. The schoolboy relapsed a month after the first attack. Since that date two distinct waves have occurred in the school and will be described separately as Waves I and II.

Wave I. In November 1929 six cases with rheumatic manifestations occurred. One (No. 250) was of Vining's (31) toxic debility type which led up to an attack of rheumatic fever early in January 1930 and a permanent mitral lesion. Another (No. 289) had pericarditis, but, although all six had joint pains, only one (No. 66) developed definite effusion. The other five were junior schoolboys of an age at which the classical picture of polyarthrititis is frequently absent, and the high incidence among the preparatory boys during this term must be noted. One school servant—an old rheumatic male—relapsed at this time and has since been invalid with auricular fibrillation.

Two months elapsed—including the first five weeks of the Lent Term—before rheumatism reappeared in the school on February 28, 1930, when boy No. 79 was admitted to the infirmary with typical polyarthrititis with effusion.

¹ Received September 4, 1931.

Ten days later boy No. 66 relapsed and thirteen other cases followed in rapid succession during the next month. Of the fifteen attacks of rheumatism in the second half of this term but three occurred in junior schoolboys—a marked contrast with the relative incidence in the two parts of the school during November and December 1929.

The shoe-cleaner relapsed on March 15, at which time she was working in the infirmary, and a few days later a master's wife with pre-existent mitral disease, who had sons in the school, developed a severe attack of rheumatic fever. Further cases in the village did not occur until the beginning of June, a month after the end of term, when an old rheumatic patient relapsed and another woman living in the same row of cottages had a first attack of arthritis and developed a persistent endocarditis. The village patients had all been in close contact with persons employed in the school.

It will be noticed that rheumatism tended to occur towards the end of term. Reference to Graphs II and III will show that this concentration was also related to a widespread incidence of sore throat in the school.

The clinical appearance of the sore throat, associated with Rheumatic Wave I, was similar to that described as lacunar tonsillitis by Frankel in 1895 (6). The most obvious sign was a dry, clean, white chalky exudate in the crypt mouth—distinct from the detritus occasionally found in the crypts. I imagine the appearance could be imitated by sprinkling a fine but opaque white powder on to the tonsil surface and then wiping the raised parts clean of dust, leaving crescents, arcs, and occasionally complete circles of white outlining the crypt mouth. Occasionally the exudate became confluent. The tonsils were not so acutely hyperaemic as the post-faucial mucosa (pharyngopalatine folds) upon which the exudate was occasionally seen in ill-defined streaks or spots. On the post-pharyngeal wall the lymphoid nodules were always bright red, and frequently specks of 'growth', sometimes an eighth of an inch in diameter, opaque, white or grey, with hazy indistinct outlines, were observed. These 'hazy specks' occurred more frequently in boys without tonsils—doubtless because tonsillectomy is usually followed by a definite increase in the amount of these pharyngeal granulations, and the exudates of acute sore throat have a predilection for lymphoid tissue (7, 8).

The exudate was seldom obvious at the beginning of pyrexia but developed within the first two days. The mean duration of pyrexia was about three days, and the 'lacunar' tonsillitis disappeared in four to five days; except in a few instances, notably one boy, in whom it was still present, although symptomless, five months after the original infection. The onset of pyrexia was usually marked by chill without subnormal temperature. Complaint of sore throat was in many cases only elicited after a leading question had been asked. Aches in the lumbar region and the extremities were common, and in a few cases precordial or thoracic pain was severe but of short duration. Headache was fairly constant but, in the absence of sinus infection, relatively mild. Epistaxis was rare. The boys were content to be still and did not

choose to read or play games during the pyrexial period—this in marked contrast to other types of sore throat. A flushed moist skin was the rule, associated sometimes with drenching sweats. Papular urticaria occurred a few times, and mild purpura simplex, without rheumatic manifestations, was observed twice. The description, 'feverish cold', would have fitted most cases, but the boys were considerably debilitated by the attack, and had to be kept off games for longer than is usual with other simple nasopharyngeal catarrhs. Systematic bacteriological investigations were not attempted, but frequent swabs examined either by Dr. Taylor or Dr. Eastes indicated a fairly constant flora of haemolytic streptococci in the school during the prevalence of lacunar tonsillitis. This was confirmed in greater detail by Dr. Griffith, working in connexion with the Committee for the investigation of nasopharyngeal epidemics in public schools. I am grateful to Dr. Griffith for the following reports:

On December 17, 1929, swabs were received from the ears and throats of three boys and in every instance haemolytic streptococci were obtained in culture. An agglutinating serum was prepared in a rabbit with the ear strain from one boy, 'Beatty', and in six weeks a type-specific serum of moderately high titre was obtained. This serum was used to test the strains of haemolytic streptococci which had from time to time been found in throat and ear infections occurring at 'X' School.

It was shown by simple agglutination tests, and confirmed by agglutinin-absorption experiments, that . . . of eight tonsillar and pharyngeal swabs received on March 27, 1930, from boys in whom tonsillitis was followed by joint pains with more or less definite effusion and signs of 'rheumatic' carditis, five yielded haemolytic streptococci of a serological type identical with the 'Beatty' strain.

Haemolytic streptococci had been but rarely detected in occasional throat swabs during at least three years prior to December 11, 1929, when they were first found during Michaelmas Term. The first recorded appearance of haemolytic streptococci during Lent Term 1930 was on February 22, but there is clinical evidence of their presence before these dates, although not for any great length of time. After these dates they were found in almost every swab, and the association of haemolytic streptococci, particularly the 'Beatty' strain, with the lacunar tonsillitis and the rheumatism which occurred *pari passu* in this wave was, on clinical grounds, very convincing. Of the cases from which swabs were taken on December 27, 1930, six (Nos. 32, 281, 278, 293, 7, 52) are included in Table I. Four of these yielded the 'Beatty' type of haemolytic streptococcus, one (No. 278) a *Streptococcus viridans* virulent for mice, and No. 7 no streptococci. All these boys had been isolated for an average of thirteen days since the onset of disease, a period sufficiently long to permit the disappearance of an infecting organism from the throat (9).

Wave II. Over ten months elapsed before rheumatism again appeared in the school: a year after his original attack, boy No. 79 was troubled with severe joint pains with little or no effusion and no pyrexia. On March 10,

1931, boy No. 251, who had complained of sore throat while warded with chicken-pox in the middle of February, developed signs of carditis with fleeting joint pains but without effusion. On the following day boy No. 20 developed monarticular effusion and carditis. On March 20 boy No. 18 had a carditis with high fever and joint pains, but without effusion. At this time a sore throat in boy No. 250 had developed into a quinsy, which was followed ten days later by a relapse of polyarthritis and serious exacerbation of heart symptoms. Boy No. 20 relapsed about March 20 while at home, and boys Nos. 314 and 232 were attacked with acute rheumatism within a few days of returning home from school, the latter suffering from erythema nodosum, associated with effusion into his joints, and transitory carditis. Of these seven patients five had not returned to school four months after the onset of their disease, four had acute rheumatism, one subacute rheumatism, and two probable rheumatism.

Twenty-seven per cent. of the school during the Summer Term were attacked with sore throat and the clinical signs of the tonsillitis which accompanied Wave II of rheumatism. The attack was less abrupt than that of Wave I, and the pyrexia less marked, frequently with a rise on the second or third day. Tonsillar exudate took two or three days to develop and was less distinctively chalky, being 'greyish' or 'milky' and more jelly-like than powdery. It gave rise to foetid breath more frequently than the typical throat of Wave I, and was commonly accompanied by epistaxis and painful enlargement of the cervical glands—both conditions noted as rare during the previous epidemic.

An extensive bacteriological investigation was kindly undertaken by Dr. Griffith of the Ministry of Health, and his results are compared with the clinical findings in Graph III. Throat swabs from 105 patients warded with febricular, feverish cold, or sore throat were examined. During the first twenty days of the term pneumococci predominated, but later haemolytic streptococci concentrated, and of 77 strains of haemolytic streptococci grown, 67 were of an identical serological type distinct from the 'Beatty' strain and referred to as type H+ in this paper. This concentration of H+ streptococci signalled the onset of the second wave of rheumatism, and the organism was present in the throat of each of the seven cases recorded.

Haemolytic streptococci had been relatively scarce at the end of the previous term. A swabbing experiment was performed between December 3 and December 9, 1930. Of fifteen swabs from pyrexias of nasopharyngeal origin haemolytic streptococci were numerous in four, a few colonies were found on a fifth plate, and one colony on a sixth. Only two strains were identified serologically, and both were of the 'Beatty' type. It is probable that H+ streptococci were new to the school at the beginning of Wave II.

To sum up, twenty-nine attacks of rheumatism were observed in a semi-isolated community of about 340 boys between May 1929 and April 1931. These cases were distributed in two main waves and involved 25 boys—there being four relapses.

	Wave I (22 attacks) Nov. 1929-Apr. 1930.	Wave II (7 attacks) Mar.-Apr. 1931.	Total.
Acute rheumatism	7	4	11
Subacute rheumatism	8	1	9
Probable rheumatism	7	2	9
Including erythema nodosum with rheumatism		1	1
" chorea with rheumatism	1	—	1
Carditis	15	5	20
" with endocardial bruits	6	1	7
" with extracardial bruits	4	—	4
" with appreciable effusion	1	—	1
Hearts not yet recovered	5	2	7
Including hearts permanently damaged	5	?	5

A more detailed analysis of these figures is presented in Table 1.

The classification adopted by the Ministry of Health (10) has been used—a temperature above 101° F. indicating acute, and below that subacute rheumatism. Cases presenting polyarthritides with effusion are included in these groups, other rheumatic manifestations being classed as 'probable'. Growing-pains without carditis are not classified as rheumatic, neither are the back and shoulder aches and thigh pains common to certain nasopharyngeal infections. Although effusion was more easily detected in the knees and ankles, the upper extremities were as commonly affected as the lower, with motionless hands, pale, sodden, lack-lustre, skin relieved by bright pink patches over the joints.

The diagnosis of carditis was made on the presence of dilatation with diffuse apex beat and blurred first apical sound irrespective of pulse-rate. An increased pulse-pressure with low systolic reading was commonly observed, and precordial pain was frequent. Bruits classed as *endocardial* were of the soft short myocardial type except in two cases—Nos. 278 and 246—in which transmitted murmurs developed within three weeks of the onset of the disease and have persisted. In three cases short clicking extracardial bruits were heard repeatedly a little mesial to the apex beat. In a fourth (No. 293) a widespread to and fro shuffle preceded the onset of a pericardial effusion, and this boy has since developed a persistent systolic bruit.

Epidemic Sore Throat

Apart from frequent records of milk-borne epidemics of streptococcal sore throat there has been little written on the clinical aspect of simple streptococcal nasopharyngitis. I have attempted to discuss the subject in another paper (11), and my impressions may be summarized as follows:

The disease is commonly an acute droplet infection. Autogenous infections are infrequent. Many different types of streptococcus are responsible, but each is specific in a local sense, and four or five distinctive clinical forms have been described. A subject immune to one type of streptococcus may be susceptible to the attack of another. These types of sore throat are as

distinctive in their aetiology as scarlet fever, which is a clinical entity in the group.

Although pain and a characteristic appearance of the tonsil and pharyngeal lymphoid tissue may permit the diagnosis of streptococcal sore throat in many cases, a simple coryza or febricula may be the only sign of invasion even when a marked nasopharyngeal reaction is present. Actual pain is frequently absent and sore throat may not be complained of. This fact is of importance in relation to acute rheumatism, since many writers make much of the absence of a history of sore throat in acute rheumatism seen after the attack as evidence that the nasopharynx is not the portal of entry. Case to case spread of sore throat is sometimes difficult to prove, for the immune carrier plays a large part in the dissemination of the organisms. Bloomfeld and Felty (12), working on a haemolytic type, and Kirkbride and Wheeler (13) on scarlet fever, give case examples with bacteriological confirmation of immune carrier transmission, and the recent work of Glover and Griffith (14) provides absolute proof of this phenomenon.

Even in the absence of an epidemic the frequency of acute throat is well known to the general practitioner and the casualty officer. Close (15) has reviewed this subject, and shows that 15 per cent. of all first attendances in the Casualty Department at Guy's Hospital are on account of acute throat. Nasopharyngitis, febriculae, and pyrexia of uncertain origin are not included, and the incidence of acute upper air-passage infections is probably treble (16) that figure.

An important consideration in these conditions is that although the infecting organisms may be found in deep tissues the surface is their main habitat and the infection is comparatively short lived.

Scarlet streptococci are lost from the throats of scarlet-fever patients in from three to four weeks (17), provided the patient is not retained in hospital where he can be reinfected (18, 19); this probably explains the long duration of the carrier state in a closed community.

Bloomfeld and Felty (20) remark that carriage of their β -haemolytic streptococci in the throat protects against the pyrexial disease produced by them, yet in susceptibles one attack may not protect, but the organisms disappear.

Although tonsillectomy removes the possibility of anatomical tonsillitis, it does not control acute nasopharyngeal infections by organisms which would give a clinical tonsillitis if the tonsils were present (11).

The two waves of rheumatism described in this paper were accompanied by epidemics of sore throat having different causes and producing distinctive clinical appearances. In this connexion it is interesting to note that Riesman and Small (21) state that throats infected with *S. cardioarthritidis* show inverted crescents of hyperaemia on the anterior pillars and uvula. There is an excess of transparent mucus but no opaque exudate on the tonsil—the whole throat is at first brilliant red, but later vertical streaks of a bluish tinge are seen on the anterior pillars, and the post-faucial folds of mucosa have a deep red velvety appearance. This organism, of which the aetio-

logical relationship to acute rheumatism is accepted by many authorities, is said to 'prefer the surface' and accordingly to grow in locations which are not removable by surgical means.

Haig-Brown's (22) 'rheumatic tonsil' presented 'little green dots studding the tonsil surface—in more severe cases the whole tonsillar surface covered with a greenish mass'.

I have failed to find a description of the appearance of the tonsil in the acute stage of *Diplococcus rheumaticus* (Poynton and Paine) rheumatism, but, from the literature, one obtains a general impression that a follicular tonsillitis is most commonly met with. Coombs (23) remarks, 'routine examination of the outward appearance of the tonsil in a great many rheumatic children has convinced me that there is no special type of gross anatomical change associated with rheumatic infection'.

Epidemiology of Lacunar Tonsillitis complicated by Rheumatism

Graphs II and III represent admissions to the school sanatorium for nasopharyngeal infections, mainly pyrexial colds and sore throats. Each marked square represents a new case. The preparatory school, although housed in the same building, is separated from the upper school as far as practicable, although this segregation is not absolute. The two portions of the school are charted separately.

Michaelmas Term, 1929 (Graph II), opened with an appreciable wave of common cold in both schools. This wave had faded by the end of the second week of the term when a new form of sore throat with the features of lacunar tonsillitis began to appear in both schools. The upper school suffered little—thirty-one pyrexias in fourteen days with eight typical cases—and for the remaining month of the term was healthy, except for five cases of common cold. The story in the junior school of ninety boys was very different. In the first fortnight following the appearance of lacunar tonsillitis nine typical cases occurred amongst thirty-six admissions for pyrexial nasopharyngitis. The morbidity continued at about the same level until the end of the term, but the disease increased in virulence and produced 60 per cent. typical cases during the last two weeks of term, including 20 per cent. complicated by otitis media.

The incidence of rheumatism was proportionate to the morbidity from pyrexial nasopharyngitis and is indicated in the diagrams. One mild case (boy No. 66) occurred in the upper school, but five small boys had definite rheumatic manifestations (see Table I). The school environment is common to both groups of boys. Food, clothing, housing, care, heating, lighting, water, air, weather, and exposure are constants in all cases. The only variants are those associated with the persons of the boys; and the occurrence of a high morbidity in one part of the school while the other is free from disease admits of one conclusion only—the school's illnesses during this period, including rheumatism, appear to be phenomena of direct contact.

Graph III shows how Lent Term, 1930, opened with a healthy nine days,

but, unfortunately, two separate and distinct strains of measles were introduced—one into the junior and one into the upper school. In due course the mass attack of measles followed, and exhausted itself in one wave and a few trailers. Prior to the main measles wave lacunar tonsillitis had also reappeared in both schools, which, with its abortive forms, persisted and became well established in the upper school. The junior school, probably immunized by the Michaelmas epidemic, soon freed itself from this infection and was moderately healthy for the second half of the term. The morbidity of the upper school increased and fifty cases (in 250 possibles) occurred in each of the last two fortnights of the term. Infectiousness appeared to become greatly enhanced about March 10 and the sanatorium staff was decimated; in spite of this the case-incidence remained sub-epidemic throughout and no influenza-like steeples were observed.

Rheumatism again occurred in direct ratio to the nasopharyngitis waves, but during this term the upper school was involved, with two exceptions in junior schoolboys, viz. boy No. 7, a relapse, and boy No. 322, who is the brother of boy No. 52, from the upper school.

Notes on Other Possible Aetiological Factors

It may be suggested that measles had lowered the resistance of the school or that the rheumatism was a direct consequence of measles. There are two strong arguments against this association: (1) rheumatism appeared before measles was introduced into the community, (2) measles attacked but a small proportion of the rheumatics—the attack rate being about the same in measles and non-measles patients. It is, however, obvious that the persistent cough of measles is a fine instrument for ‘spraying’ and tends to increase the spread of new infections.

The food at the school is beyond reproach. The boys’ diet is unlimited and well balanced. During Lent Term meat is occasionally withheld on two fast days in each week, but is replaced by fish served with added animal fats in sauces if not fried in animal fat. The usual seasonal variations in diet are present, but any deficiency in green vegetables is made good by an increased ration of fruit. Boys are encouraged to take drinks of fresh milk which is always available. Butter substitutes are not used in the school. New-laid eggs are served daily and cod-liver oil is consumed in large quantities. There can be no vitamin D deficiency. A seasonal variation in fat-soluble A and the vegetable vitamins is probably present, but is made good in most boys by direct feeding of vitamin preparations. Warner’s (24) suggestion that avitaminosis is an appreciable factor, related as closely to acute rheumatism as it is to rickets, cannot be supported. It is, however, of considerable importance in so far as lack of vitamins lowers the resistance to nasopharyngeal infections. Thomson and Edgar (25) state that the ‘results of experimental feeding lend no support to the belief that diet is of material importance in the aetiology or course of rheumatism in children’.

No observations on the effect of heredity have been made, but it is interesting to note that two brothers (boys Nos. 52 and 322) were attacked within a few days of each other.

There was no evidence of bites from *Ceratophyllus fasciatus* or any other flea (26).

In this school it is almost impossible for boys to sit about in damp clothes or shoes. Gum-boots are worn during rambles or on the touch-line, and warm sprays are popular after games and when boys change from 'knockabouts' to the regulation suits worn in school.

The *meteorology* of the periods under review was closely studied, but no significant relationship appeared other than some slight support for Richter's (27) association of nasopharyngeal disease with the 'trough following a ridge of high-barometric pressure'. I think it should not be forgotten that such troughs coincide with high humidity readings, and a high humidity favours droplet infections. Miller (1) and Thomson (28) have demonstrated the influence of damp on the incidence of acute rheumatism, but do not emphasize the fact that damp is a common factor having a measurable influence on the spread of all droplet infections. It would appear to be reasonable to relate the seasonal incidence of rheumatic fever to this factor, after due allowance has been made for the overcrowding and 'hibernation' which accompany the increased humidity of the rheumatic months.

Condition of the Tonsils

During the past year much has been written to shake a widespread belief in the value of tonsillectomy in rheumatism (29). The condition of the throats in my small series is compared with the mean of the school in the following table. These data were collected at midsummer 1929, or at the time of admission to the school if since that date, but prior to the appearance of rheumatism in the school (48):

Condition of the Throat in Health (289) Boys

	All cases.		Never ill.		Habituals.*		Subsequently Rheumatic.	
	No.	%.	No.	%.	No.	%.	No.	%.
Total number	289	—	60	21 ± 1.6	50	18 ± 1.5	25	7 of 330 ± 1.3
Tonsils:								
present	122	42 ± 2.0	22	37 ± 4.2	21	42 ± 4.7	8	32 ± 6.2
large	59	22 ± 1.6	8	13 ± 2.9	11	22 ± 4.0	1	4 ± 2.6
removed	167	58 ± 2.0	38	63 ± 4.2	29	58 ± 4.7	17	68 ± 6.2
Remnants:								
present	120	42 ± 2.0	23	38 ± 4.2	18	36 ± 4.6	12	48 ± 6.8
large	66	23 ± 1.7	14	23 ± 3.7	8	16 ± 3.5	4	16 ± 4.9
Pharyngeal granulations	101	35 ± 1.9	21	35 ± 4.2	20	40 ± 4.7	9	36 ± 6.5
Cervical glands:								
palpable	123	43 ± 2.0	29	48 ± 4.4	18	36 ± 4.6	13	52 ± 6.7
large	82	28 ± 1.8	18	30 ± 4.0	11	22 ± 4.0	6	24 ± 5.8
Unhealthy throats	23	8 ± 1.1	6	10 ± 2.6	5	10 ± 2.7	3	12 ± 4.4

* *Habituals* = boys excluded from school with pyrexial nasopharyngitis at least three times during the four school terms ending midsummer 1929.

The possible error in these figures is considerable, and it would appear that tonsillectomy has had no influence on the incidence of rheumatism.

Rheumatic Diathesis

I am unable to find evidence of a physical diathesis in my series, but the following figures are available with regard to the colouring of my patients :

Of 230 healthy boys . . .	161 had fair hair	} Ratio 0.73
	117 had pigmented irises	
Of 25 rheumatics . . .	18 had fair hair	} Ratio 0.83
	15 had pigmented irises	

Discussion

Glover (3) in his Milroy lectures writes : ' In the case of acute rheumatism epidemics an "unseen" carrier wave is probably present, but in addition there are two "visible" waves, the larger the tonsillitis wave and the smaller the acute rheumatism wave.' This phenomenon is clearly demonstrated by the events described in this paper, and Glover's text, 'restating the incidence of acute rheumatism (notwithstanding its low infectivity) as the incidence of a specific infectious disease conveyed by droplet infection', is, broadly speaking, confirmed. The specificity of the infection is, however, in doubt, and the identification of two distinct strains of haemolytic streptococci in association with acute rheumatism is of particular interest.

It is commonly held that the causal organism of acute rheumatism belongs to the viridans group, although the indifferent streptococci have also been suspected. That rheumatism may follow scarlatina is well known, and if this sequela is attributable to the scarlatinal streptococci there appears to be no obvious reason why non-scarlet haemolytic streptococci should not contain a rheumatic factor (e.g. bacterial endotoxin) in common with the scarlet fever types. Parish and Okell (30) have shown that Dick toxin is by no means a peculiarity of scarlet-fever strains, but is produced by all human haemolytic streptococci in a greater or lesser degree. It is unlikely, however, that Dick toxin is the rheumatic antigen in scarlatinal rheumatism. Dochez and Stevens (31) find that the injection of exotoxin neutralized with scarlet-fever globulins may cause arthritis in susceptible animals after a period of about fourteen days.

Birkhaug (33), Irvine-Jones (34), and Collis (37) have demonstrated a cutaneous hypersensitiveness to haemolytic streptococci in rheumatics—more marked in active than in inactive cases—but the reaction-producing haemolytic strains are less numerous than the reaction-producing viridans strains. Cecil (35) and his co-workers have actually recovered a haemolytic streptococcus from the blood and joints of a typical acute rheumatism, and more recently Schlesinger (36), Collis (37), Sheldon (38), and, especially, Coburn (9) have produced convincing evidence of this association.

The suggestion of an aetiological relationship between haemolytic streptococci and rheumatism is not inconsistent with the allergic theory of the pathology of this disease. As Jones (39) remarks, 'This hypothesis that infections, if and when present, act through the medium of anaphylaxis, far from invalidating the infective theory, would account for the disparate findings of bacteriologists'.

Small (40), who looks upon the manifestations of acute rheumatism as exudative lesions which appear when the patient begins to develop an immunity to the specific toxic factor in the organism infecting him, postulates a condition of hypersensitiveness—an Arthus phenomenon—to bacterial protein common to many groups and types of streptococci.

The work of Hitchcock and Swift (41), and Derick (42) is well known and is surveyed in their communication to the Bath Conference, 1928, while MacDonald (43) has recently produced a complete summary of the more contemporary writings on this subject. The latter also demonstrates the absence of any signs of specificity in the bacteriology of tonsils removed from rheumatics when compared with non-rheumatic tonsils, thus confirming the work of Irvine-Jones (34) who writes: 'The streptococci of the upper respiratory tract of rheumatic children are identical with those of normal children.'

In all these writings, and those of Zinsser and Yu (44), the allergic antigen is attributed to chronic streptococcal foci. Yet, if allergy is the prime factor in rheumatism, surely a series of acute contacts with streptococci will best serve the conditions required for the development of an allergic state! This important point has been appreciated by Kinsella (45) who writes: 'While the tissues are still in a state of allergy the further contact of a body with any streptococcus (or its toxin) will precipitate a critical reaction in which the small blood-vessels proliferate and a typical proliferation lesion (Aschoff body) results. The clinical expression of this reaction is the disease, acute rheumatic fever.'

There is a striking clinical demonstration of this repeated contact and consequent sensitization in the series of cases under discussion. Table I records a succession of acute nasopharyngeal infections leading up to the attack of rheumatism in the bulk of the patients. In a closed community, such as this school, it is reasonable to postulate a simple and fairly uniform flora during an epidemic, and in all probability these relapses of acute nasopharyngitis are due to the standard organism of the community at the time, the first attack having failed to establish an immunity. Table I also shows how relapses have occurred when they would be expected—at a time of streptococcal preponderance.

An incomplete immunization—a 'failure to assimilate'—is intimately related to acute rheumatism. It is the explanation of the 'pre-rheumatic state'—of Vining's (31) 'toxic debility'—in which careful observation will show a sequence of nasopharyngeal infections generally thought to be insignificant. These attacks (e.g. 'common cold', 'febricula', 'pyrexia of uncertain origin') are frequently symptomless or give signs of gastro-enteritis or

'cyclical vomiting' distracting one's attention from the portal of entry—the nasopharynx.

It is customary to look upon the pre-rheumatic states as periods of continuous absorption from foci of chronic infection. This conception calls for revision and qualification. Demonstrable foci of chronic infection are difficult to find in these states, and the characteristic periodic recurrence of pyrexia is more likely to be due to a string of new infections than to chronic foci. Thomson (46), writing of the rheumatic inmates of Baskerville School, is 'impressed with the "grouping" of these attacks which may cause deterioration in the condition of the heart . . . they tend to occur in children who are in contact in the dormitories or at meal times'. Be this as it may, Perry's (47) words ring true: 'When we have discovered the difference between complete immunity, which makes the patient safe, and the dangerous state of allergy or hypersensitiveness, which is apparently a partial or perverted immunity, we shall have discovered the key to the practical treatment of chronic streptococcal illnesses.'

Table I also shows several examples of a characteristic of acute rheumatism strongly suggestive of an allergic factor in its aetiology. I refer to the period which intervenes between the original infection when identified and the onset of joint involvement. This is particularly noticeable in scarlet rheumatism (48, 49), and Warner and Campbell (50) and Schlesinger (36) remark upon its occurrence in non-scarlet rheumatism. Light is thrown upon the meaning of this interval by the work of Dochez and Stevens (32), already mentioned, and that of Parish and Okell (30), who found that in rabbits recovered from septicaemia as the result of treatment with antistreptococcal serum-globulin a second stage of 'infection' supervenes with the production of local lesions in joints and serous sacs. 'Protection has never been obtained against this phase of the infection with any antitoxin or antiserum we have used.' It is not unreasonable to compare this phenomenon with the interval in serum disease preceding the acute rheumatism denuded of its infective characters.

A widespread parasitism of rheumatism-producing streptococci may induce a small epidemic of rheumatism in an overcrowded camp or ship or school. In a community of hypersensitives, on the one hand, such as a cardiac hospital, it will cause a more extensive outbreak, whilst at the other extreme, in the home, where its influence is obviously limited, the usual single, isolated, and apparently sporadic case of rheumatism is the most that can be expected. The onset of such a case may be preceded by attacks of the common cold or sore throat in other members of the household. Less frequently an apparently healthy member of the family with a chronic focus of infection in the nose or throat may be an immune carrier, and in rare cases antigen may emanate from autogenous chronic foci in the tonsils, intestines, or sinuses. The problem of acute rheumatism is related, epidemiologically, to the problem of the simple nasopharyngeal infections, and, physiologically, to the problem of immunity to these infections.

Should the production of immunity be incomplete subsequent contact with antigen will give rise to a pre-rheumatic state, followed, in certain cases, by a hypersensitization characterized by the manifestations of acute rheumatism. This state will be preceded by signs of a coccal invasion, separated from it by an interval. It is not necessary that the rheumatic antigen be constantly present in the nasopharynx or tissues of the rheumatic subject, and it may easily have disappeared before the onset of polyarthritis and carditis. On this assumption acute rheumatism is not necessarily an infectious disease, although the primary infecting agent is disseminated by droplet infection.

Attention is drawn, not only to the importance of certain droplet infections, but to the heterogenous nature of these infections. The prophylaxis of rheumatism, reduced to the simplest terms, requires that the pre-rheumatic and the rheumatic child shall not catch cold.

Conclusions

1. Two epidemics of rheumatism are recorded and their relation to parallel waves of haemolytic streptococcal sore throat demonstrated: the causal streptococci being of two distinct strains.

2. Survey of the epidemiological factors concerned leads to the conclusion that droplet infection was responsible for the spread of sore throat and consequently of rheumatism.

3. It is tentatively suggested that rheumatism occurred in those who, being incompletely immunized by a first contact with a rheumatism-producing streptococcus, developed hypersensitiveness (allergy) to that organism.

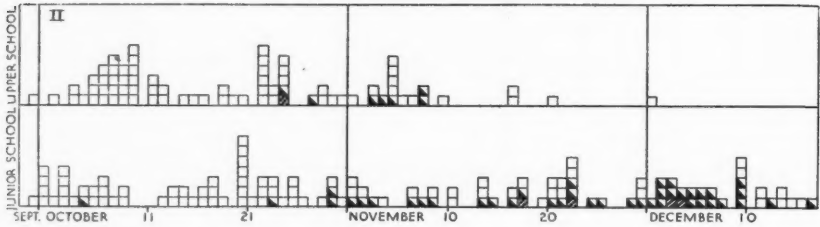
3	7	10.11.29 29. 1.30 14. 2.30 19. 3.30	A3 A3 A3 ⁴ A2	+	+	+	+	12.2		
4	239	24.11.29	A3	+	+	+	+	10.10	Had A3: 28.2.30. No joints	
5	289	16.10.29 26.10.29 5.12.29	A1 A2 A3		+			13.4	Had H+ A3: 3.3.31. Precordial pain	
6	250	10.11.29 18.11.29 6.12.29 6. 1.30 3. 2.31 13. 3.31 22. 3.31 3. 4.31 12. 4.31	A3 A2 A2 At home A A3 Quinsy At home	+	+	+	+	12.10	Vining's toxic debility type At home	
7	202	8.10.29 24.10.29 6.12.29 At home	A1 A3 * At home	+	+	+	+	14.8	* Frontal sinus At home. Doctor reports permanent rheumatic heart disease	
8	79 _h	11. 2.30 28. 2.30 18. 2.31	A A2 A1	+	+	+	+	14.11		
9	66	See Case 2 above								
10	278	28. 2.30 11. 3.30	A3 A2	+	+	+	+	14.8		
11	293	14. 3.30 Later	A2	+	+	+	+	15.0	Pericarditis with effusion	
12	221	19. 3.30	A3	+	+	+	+	15.11		
13	7	See Case 3 above						17.1		
14	32	5. 2.30 8. 3.30 22. 3.30	M A3 A2	+	+	+	+			

TABLE I (continued)

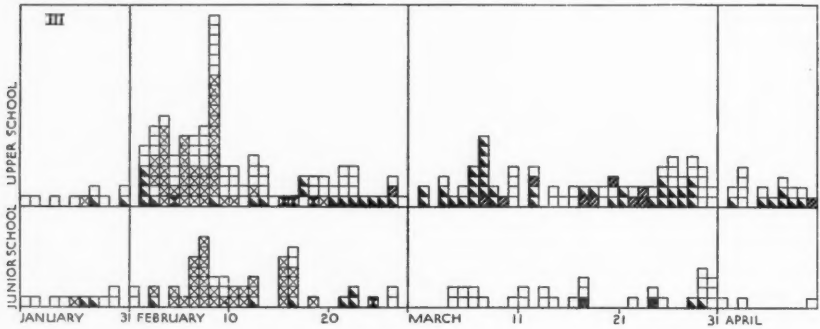
Chronological Order	Boy Number.	Nasopharyngitis.		Rheumatism.		Joints.		Carditis.			Tonsils.			Age.	Con- firmed by Doctor.	Notes.
		Dates of Attack.	Type (see Code).	Acute.	Subacute.	Probable.	Pains.	Effusion.	No bruits.	Transitory.	Endocardial.	Extracardial.	Permanent.			
15	52	5. 2.30 20. 3.30	M A3	+				+	+					15.0	Coombs Cohen	Brother of Boy No. 322
16	162	3. 2.30 9. 2.30 17. 2.30 24. 3.30	A2 M4 A3 A	+				+	+					16.3		
17	244	25. 3.30	A2			+	+						+	15.8		Nodes, May 1930
18	281	10. 2.30 12. 3.30 25. 3.30	A N2 A2					+	+				+	17.1		
19	322	26. 3.30	A2.	+				+	+		+	+	+	13.3	Cohen	Brother of Boy No. 52
20	146	22. 2.30 30. 3.30 4. 4.30	A3 A1			+	+		+				+	15.10	At home	Scarlatiniform rash. Had H + A3: 17.3.31 with mild carditis
21	26	8. 2.30	M7 At home	Chorea +				+					+	14.1	Horder	Chorea commenced be- ginning of May 1930. Relapsed 13.7.31. Haemolytic strepto- coccus in throat
22	246	11. 4.30		+				+			+		+	17.3	Gordon Coombs	Seen again 12.10.30. Permanent bruits

Excess
strep. in
stool

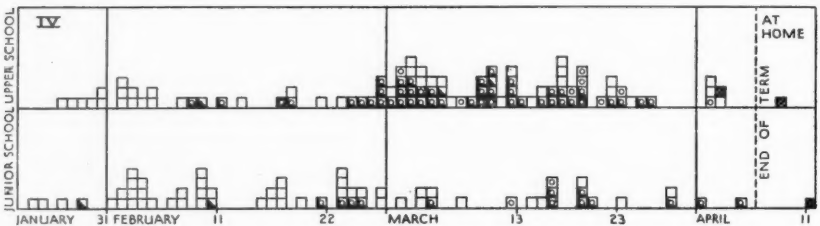
Michaelmas Term 1929



Lent Term 1930



Lent Term 1931



- Pyrexial common cold, febricula or sore throat without exudate
- Sore throat with exudate, i.e. Lacunar Tonsillitis. (*Tonsils not necessarily present. Growth frequently observed on lymphoid nodules in absence of tonsil*)
- ▨ Onset of Rheumatism included in Table I
- ▩ Measles
- ▧ Measles complicated by Pyrexial Lacunar Tonsillitis
- H+ Haemolytic streptococci of identical serological strain cultured

II. Showing a low incidence of nasopharyngeal disease in the upper school, but a high morbidity in the junior school with four cases of rheumatism. A fifth case occurred on January 6, 1930, while at home.

III. Showing a high incidence of lacunar tonsillitis in the upper school with eleven cases of rheumatism. The relative incidence of nasopharyngeal disease in the two schools is the reverse of that shown in Graph II for Michaelmas Term. Only two cases of rheumatism occurred in the junior school—one the brother of an upper school rheumatic, and the other a relapse in a boy first attacked in Michaelmas Term.

IV. Term opened with mild pneumococcal fever which was replaced by H+ streptococcal sore throat. In five cases of the latter condition diagnosed clinically the organism was not found, but was present in 13 cases not diagnosed clinically. Rheumatism occurred in proportion to the incidence of H+ streptococci.

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ADDISON'S DISEASE AND ITS TREATMENT BY CORTICAL EXTRACT¹

By S. LEVY SIMPSON

With Plates 5 and 6

THE classical experiments of Oliver and Schäffer (24) in 1895 focused attention on the active principle (adrenalin) of the medullary portion of the suprarenal gland, the symptoms of Addison's disease being attributed to its absence or deficiency. Subsequent work by Hartmann (12-16), Stewart and Rogoff (37-39), Swingle and Pfiffner (41-43), indicated that the cortex was essential to life. Adrenalin injections had no influence on the survival period of suprarenalectomized animals (cats, dogs), whereas extracts of the cortex prolonged life. Swingle and Pfiffner (42) were able to maintain life in their suprarenalectomized cats for an indefinite period. Subsequently their extract was used in Addison's disease with promising results (Rowntree and Green (34), Levy Simpson (21, 22)). Swingle and Pfiffner (42) describe the method of preparation as follows: 'The suprarenal glands (beef) packed in ice are received from the slaughter-house within twenty-four hours after the death of the animals, and the cortex dissected as free as possible from extraneous fat and medullary tissue. Ground and extracted with 95 per cent. and 80 per cent. ethyl alcohol for three or four days (one *in vacuo* at low temperature). Extract with benzene. Remove benzene *in vacuo*. Lipoidal residue extracted with acetone. Acetone removed *in vacuo*. Then distribute between 70 per cent. ethyl alcohol and petroleum ether. Latter removed by distillation. Wash, concentrate *in vacuo*; add water to desired volume. 1 c.c. represents 30 gm. of freshly dissected cortical tissue.'

The following is a detailed study of six typical cases of Addison's disease, in all of which the diagnosis was certain. One was treated with some cortical extract kindly supplied by Swingle and Pfiffner, and the remainder by cortical extract made in this country by Allen and Hanburys, according to the formula of Swingle and Pfiffner, with slight modifications. The extract was almost entirely free from adrenalin.

The Dosage of Cortical Extract and Method of Administration

Swingle and Pfiffner (42) found that the maintenance dose for their suprarenalectomized cats was about 1 c.c. to 2 c.c. a day, but should severe symptoms have been allowed to develop 6 c.c. a day were necessary to

¹ Received August 31, 1931.

secure recovery. Wilson (46) using the extract prepared by Allen and Hanburys found that 4 to 6 c.c. a day were necessary to maintain life in suprarenalectomized cats. These figures, however, offer little guidance for dosage in Addison's disease, and in fact no definite criterion of dosage in man has yet revealed itself. Blood-urea and urinary creatine and creatinine may give some indication, but with no definite consistency. The effect on symptoms and pigmentation constitute crude indications. It is conceivable that no biochemical test of dosage will be forthcoming, and that we must glean what information we can from cumbersome biological assay. In the meantime a gradual accumulation of clinical experience gives some indications.

From a limited experience the following dosage (using Allen and Hanburys' extract) is tentatively suggested. In a crisis, 50 c.c. to be given on the first day, and 20 c.c. subsequently until definite clinical improvement occurs; then 10 c.c. daily until the patient is able to walk with ease; and a subsequent maintenance dose of 5 c.c. When there is no immediate danger the initial 50 c.c. may be omitted, and in mild cases 10 c.c. a day might be the starting-point. A very concentrated extract has been used in 1 c.c. dose, but the data are at present too scanty for conclusions as to its relative potency.

The intravenous route is advisable in all severe cases during the first week, the intramuscular or subcutaneous route being used later.

If the adrenalin content of the extract is uncertain, the intravenous injections should be given very slowly. At the time of commencing this work severe adrenalin reactions were sometimes met with, but subsequently the cortical extract was almost completely free from adrenalin. This was indicated by the complete absence of any reaction, or of any rise of blood-pressure, or of blood-sugar, following the intravenous injection of 10 c.c. of cortical extract. C. J. Eastland of Allen and Hanburys found the adrenalin content by Folin's method to be 1:170,000. The ammonium molybdate method gave much higher values, probably due to a reaction with substances other than adrenalin. Biological assay gave the adrenalin content, as measured by its effect on blood-pressure, as less than one in a million. This is in keeping with the clinical findings.

Intramuscular or subcutaneous injection of the cortical extracts at first produced pain or burning, which was alleviated by very slow injection or by adding novocaine. Cresol, 0.3 per cent., prevented pain, but was discarded owing to the large quantities of extract used, and the possibility of accumulated toxicity. Norman Evers of Allen and Hanburys succeeded in obviating pain by bringing pH to 7, adding 0.2 per cent. chlorbutol, and sufficient sodium chloride to render the solution isotonic.

Clinical experience and general considerations of hormone therapy indicate the necessity for continued administration of cortical extract. In patient 1, however, good health was present eight months after the last injection of cortical extract. Menopausal changes are probably occurring in this patient,

and in a previous paper (Levy Simpson (22)) a readjustment of ductless-gland balance was suggested as an explanation. Swingle (40) found that dogs in heat or pregnancy survive suprarenalectomy for sixty-five days in contrast to the usual survival period of ten days. In patient 6, the onset of symptoms of Addison's disease occurred a few months after the menopause.

Case Reports

Case 1. M. S., a female, aged 51, was the mother of three healthy children. A fourth child had died from tuberculous meningitis in 1916. The patient's brother had died from pulmonary tuberculosis. The patient herself had been a healthy woman until the present illness.

The onset of pigmentation in this case was the earliest sign and preceded the other symptoms, as sometimes happens in Addison's disease, by many years. Pigmentation was first noticed after the last pregnancy in 1917, but apart from occasional vomiting there were no other symptoms until May 1930. At this time the patient began to feel weak and listless and the pigmentation, which had persisted since 1917, became much more intense. An attack of tonsillitis, of several days' duration, occurred in August 1930 and caused an exacerbation of the disease, resulting in increased asthenia, anorexia, nausea, retching and vomiting, apathy, and defective memory, with further deepening of pigmentation. There was some abdominal discomfort with constipation and intermittent diarrhoea. The legs and knees were painful. In October 1930 there was a further decline, the diagnosis of Addison's disease being made, and the patient removed to a nursing home on October 14. The pulse at this time was rapid and feeble, and the blood-pressure 94 systolic, 78 diastolic. The patient complained of pains in the back between the shoulders and of pain in both eyes, with inability to stand the light. Bilateral conjunctivitis was present. She spoke in a very weak voice, was unable to give a coherent history, and was completely confused as to dates. The treatment at this time was symptomatic, together with glucose enemata every four hours. On October 24, at 10 a.m., a pint of intravenous glucose (10 per cent.) was given, and at 1 p.m. the patient collapsed, lost consciousness for a minute, and had transient tonic convulsions of the whole body. There was a slight improvement on the next day, but after this the condition became progressively worse. Vomiting, headache, and photophobia were very troublesome symptoms. On November 3, hypodermic adrenalin and whole gland by mouth were commenced without appreciable benefit resulting. The patient was too ill to be removed to hospital (40 miles) and was seen by the writer for the first time on November 12 at the nursing home. The patient was then in a weak, collapsed, semicomatose condition, taking no notice of our entrance into the room, but replying sluggishly to questions on being roused. The blood-pressure was 86 systolic, 65 diastolic, the heart-sounds distant, and the pulse rapid (100) and feeble. The temperature was subnormal. The patient was thin, but not emaciated. The pigmentation was intense and diffuse, being especially well marked on the face and neck, anterior surfaces of forearms, dorsum of hands and knuckles, axillae, groins, anal clefts, waist-line, linea alba, hips, internal malleoli, and internal condyles. The palms of the hands escaped pigmentation in characteristic fashion, the creases on the flexure surface of the knuckle-joints showing as brown lines on a white background. The

pigmentation of the buccal mucous membrane was most marked and there was also some pigmentation on the gums. Examination of the chest and abdomen was negative. The patient fainted during the examination, which was only a very brief one. The temperature was subnormal, 97° F., and there was slight albuminuria. The Wassermann reaction was negative.

Effect of cortical extract. On November 12, 1930, treatment with cortical extract was started. The preparation was one made by Swingle and Pfiffner themselves at Princeton. It was given intramuscularly in doses of 6 c.c. twice a day for four days. On November 13 there appeared to be slight improvement; on the 14th a little food was taken with subsequent slight vomiting; on the 15th the patient was definitely stronger, no vomiting, less conjunctivitis, pigment fading; on the 16th improvement continued, less irritable; on the 18th very marked change for the better, cheerful and optimistic, sitting up in bed, asking for and taking food, no vomiting, no conjunctivitis, no photophobia, considerable fading of pigment. There was no appreciable change in the blood-pressure. On November 19, in the absence of further supplies of cortical extract, a modified Muirhead regimen was started, namely, 5 minims of adrenalin hypodermically night and morning, and 2 gr. (equivalent of 10 grm.) of desiccated suprarenal gland by mouth, night and morning. Improvement continued, and on November 25 patient got up for the first time for many months. On December 6 the patient began to walk. There was a slight elevation of blood-pressure, systolic 100, diastolic 74. On December 18 she was able to journey to London and be presented at a meeting of the Royal Society of Medicine. She then returned to her home and continued in comparatively good health. In January 1931 she appeared to develop a hypersensitivity to adrenalin, on one occasion with marked tremors, palpitations and collapse following five minims of 1/1000 adrenalin hypodermically. She passed large quantities of urine after this collapse. On January 17 all treatment was stopped. On January 27 the patient stated that she felt as well as before her illness. Her blood-pressure was then 98/72. From February 1 to 5 the patient took two tablets of dried suprarenal extract a day. There was apparently no particular reason for resuming the tablets except belated menstruation. It is interesting to note that palpitations and tremulousness followed the taking of the tablets by mouth, and they were discontinued on February 5. At this time the patient was feeling very well, doing her own housework and cooking, and going out for long walks. She had put on several pounds of weight and was feeling well and happy. On February 17 blood-pressure was 108/80; March 2, 110/82. On March 23 there was a temporary relapse with dyspnoea, lassitude, and conjunctivitis. The blood-pressure was then 102/70. The taking of suprarenal dried gland by mouth coincided with the recovery from this relapse, the duration of the latter being ten days. The blood-pressure on March 30 was 100/78, on April 14, 120/90, and again on the 16th, 122/72. The patient then stopped the tablets, and, in fact, all forms of therapy were discontinued from this time. Progress, however, continued, and at the present moment (August 1931) the patient is leading a moderately active life and enjoys good health. The pigmentation is still quite characteristic of Addison's disease, but of much less intensity than before treatment. Dr. Stratford Collins kindly informs me that from April till end of July the blood-pressure has remained between 90 and 120, tending to fall about the time of menstruation, there being also a slight clinical relapse at these times. The menstrual history in this case is not uninteresting. Until December 1930 it was quite normal for this particular patient,

namely, of five days' duration with three weeks' intervals. In December there was an excessive menstrual flow. Similarly in January, the occurrence being premature. Menstruation on February 21 was very slight and three weeks overdue. March 11, there was an excessive menstrual flow. During each menstruation there was a tendency to temporary relapse. In April and May there was very slight menstrual flow, but in June and July menstruation approximated to normal for this particular patient.

Case 2. C. D., a female, aged 42, was admitted to the London Hospital on February 3, 1931. She was apparently quite well apart from recurrent attacks of mild appendicitis until July 1927 when appendicectomy was performed. A few weeks later she noticed pigmentation of the abdomen over the area where the skin had been painted with iodine. In January 1928 pigmentation occurred over the dorsal aspect of the proximal phalanges and gradually spread upwards. Pigmentation also appeared on the face. In August 1928 the patient began to tire easily and felt unwell. She went away for a rest and a holiday. In October 1928 she was very weak and chronically nauseated. Menstruation became scanty and irregular. The pigmentation increased. These symptoms continued with slight periodic remissions until September 1930, when she entered St. Bartholomew's Hospital under Dr. Geoffrey Evans, who made the diagnosis of Addison's disease. The blood-pressure at that time was not low, 114 systolic, 70 diastolic. Radiography showed a calcified right suprarenal gland. Systolic blood-pressure readings during the first few months were 114, 120, 108, 100. There was some spontaneous remission of symptoms during this period but no approach to normality. The patient was very sensitive about her pigmentation and was reluctant to meet people. She was easily annoyed and could not bear an argument. There was a tendency to irritation of the skin. Occasional attacks of conjunctivitis occurred. She was very finicky about her food and her appetite was poor. She felt the cold very much and was very susceptible to the presence of draughts. She was admitted to the London Hospital through the courtesy of Dr. Geoffrey Evans and Dr. A. H. L. Thomas, her medical attendant. On examination the patient appeared very pigmented and rather thin with deep underlined orbits. There was also some concentration of pigment on the sides of the nose. Bluish pigmentation was present on the buccal mucous membrane, especially opposite the point of contact of the teeth, and also on the inner margin of the lips and around the gums. The neck was moderately pigmented, the chest was hardly affected except for the nipples which were almost black. The abdomen presented deep pigmentation demarcating a broad waist-band, the depth of colour fading as the midline was approached and being at its maximum in the loins. The navel was deep brown, and the linea alba was pigmented from the pubes to the xiphisternum. In the pelvis the pigmentation was marked on the lateral aspect of the hips. On the back there were two bands of pigmentation running from second dorsal spine downwards towards the shoulders. The spines of all the vertebrae were clearly demarcated by an overlying brown patch of skin. The buttocks were not markedly affected except for the anal cleft. The thighs escaped pigmentation, which was, however, present on the anterior aspect of the legs, dorsum of feet, and both malleoli, especially internally. In addition there was an extensive mottling of the legs caused by warming them in front of the fire two months ago, but the pigmentation was of a depth and intensity far in excess of that which may occur in normal individuals in

similar circumstances. The soles of the feet were not affected. The axillae were slightly coloured, but the upper arms were almost normal. The back of the elbows, the forearm, especially its dorsal aspect, and the back of the hands, particularly the knuckles, were deeply pigmented and there was a tendency to desquamation. On the anterior aspect of the forearms the pigmentation stopped very abruptly at the wrist, the palm and anterior aspect of the fingers being white in contrast except for the pigmented clefts and creases. The blood-pressure on admission was 95 systolic, 75 diastolic. The remainder of the examination was essentially negative, as was also the Wassermann reaction.

Treatment with cortical extract was commenced on February 9, the patient receiving 10 c.c. daily intramuscularly for the first two weeks and 5 c.c. daily subsequently, except for a few days in the fourth week when 10 c.c. was given. After the first week the patient felt stronger, her appetite increased, and the pigment was seen to fade. The improvement steadily continued during the next few weeks, but there was a loss in weight from 6 st. 5 lb. to 6 st. This is probably attributable to the numerous investigations which were carried out, many of which required fasting until midday. The pigment was demarcated on a graduated scale of colours, which clearly demonstrated its diminution. This was enthusiastically confirmed by observations of friends of the patient. The blood-pressure at first was unaffected, systolic readings being between 85 and 95; but on March 7, the blood-pressure rose to 110 systolic, 80 diastolic.

The patient left hospital on March 16, continuing the injections herself, and was seen again by me on April 7. She then appeared very much better. The pigmentation was much less and her face appeared fuller and fatter. She had gained 5 lb. in weight. She walked into hospital carrying her own suit-case and expressed a desire to return to her occupation. Her appetite had improved enormously so that she was able to eat greens and fat, which she had not touched for many months. The sensation of chilliness was much less troublesome than hitherto. She walked for long distances without fatigue and felt like 'dancing an eightsome reel'. She was now able to meet strange people with composure and to mix with crowds. She was no longer fractious or petulant, and was altogether in very good mood. She remained in hospital for a few days for some investigations and then returned to her home a few hundred miles away where she continues to progress. Her blood-pressure on leaving, however, (April 9) was only 100 systolic, 70 diastolic. On May 29 the patient wrote to say that she was still doing well and that her weight continued to increase: 'Pigmentation on face two shades lighter when compared with your chart, neck same as face; hands almost normal; abdomen one shade lighter; knees still dark; legs from knee to ankle pigmentation nearly gone; feet same, heels still very dark—I am eating and sleeping well and can do all the work of the house which I certainly could not do a year ago.'

A letter in similar strain was received on August 25.

Case 3. T. W., a plumber, aged 19, was admitted to the London Hospital on December 30, 1930. There was a history of a febrile illness in 1927, diagnosed as pleurisy. A complete recovery occurred within three weeks and the patient was then apparently quite well until August 1930. He then began to tire easily and to lose weight rapidly. About the same time he experienced some pain in the left side of the chest and was sent to the Royal Chest Hospital for advice. He attended for some weeks as an out-

patient, but became progressively weaker and suffered from attacks of faintness, vomiting, and drowsiness. On November 17, 1930, he was admitted to the Royal Chest Hospital as an in-patient under Dr. A. W. Stott, who made the diagnosis of Addison's disease. The onset of pigmentation appears to have been insidious, but more or less concurrent with the other symptoms. The systolic blood-pressure varied from 74 to 92 mm. of mercury and the diastolic from 46 to 52. There was no clinical or radiological evidence of pulmonary tuberculosis. No lead was found in the urine. The patient was placed on a modified Muirhead regimen for several weeks: adrenalin $m \times$ of a solution 1/1000 subcutaneously three times a day, and ephedrin gr. i by mouth three times daily. There was some resulting gain in strength, and slight general improvement, but 8 lb. loss in weight. On December 30, by courtesy of Dr. Stott, he was transferred to the London Hospital for treatment by cortical extract. On admission the patient was seen to be wasted and ill with deeply sunken pigmented orbits. In spite of obvious weakness and inability to sit up without resulting faintness and giddiness, he was very restless and excitable in bed, simulating at times a hyperthyroid state. Contrary to the characteristic findings in Addison's disease, his appetite was ravenous. The pigmentation was diffuse, being especially well marked over the face and neck, the collar-stud impressions, the vertebral spines, bony projections of the shoulder girdle, dorsal aspects of elbows, forearms, and knuckles, hips and buttocks, patellae, and inner malleoli of ankles. The palms escaped pigmentation except for the phalangeal flexures and palmar creases, but the soles of the feet were moderately pigmented. There was a diffuse pigmentation of the trunk and a tendency to desquamation over the whole body. The buccal mucous membrane, the gums, and the lips were pigmented. The blood-pressure was 90 mm. of mercury systolic and 50 mm. diastolic. The remainder of the clinical examination was essentially negative, as was also the Wassermann reaction.

Course of events in hospital. Treatment with cortical extract was commenced on January 1, 1931, 4 c.c. being given intramuscularly twice a day. By the end of the first week there was a definite gain in strength and fading of pigment. This progress continued, and on January 12 the patient was able to get up for an hour without any feeling of weakness or dizziness. By January 17 the general condition was so good that the patient stated that he felt 'like ten men'. There was, however, hardly any gain in weight, although it must be remembered that he had been subjected to several tests which necessitated starving for many hours. During the next week he gained 9 lb. in weight. On January 20 the dose of extract was reduced to 4 c.c. once a day intramuscularly. The patient continued to remain in good condition. He got up every day, helped to serve teas in the ward, walked about with ease, and expressed a strong desire to return to work. The blood-pressure throughout this period had not shown any definite rise, but on the day of discharge from hospital, January 26, the systolic reading was 110 mm. and the diastolic 65 mm.

The patient continued the injections of extract at his home and reported to hospital every few days. On February 6 he complained of a sore throat and slight cough. His temperature was then 100.6°F ., systolic blood-pressure 105 mm., diastolic 65 mm. His throat was inflamed and hyperaemic. He was admitted to hospital with the diagnosis of 'influenza'. The next day he was coughing small amounts of muco-purulent sputum and numerous rhonchi were heard all over the chest. On February 10 the temperature rose to 103.5°F . and the patient was nauseated and listless. The dose of

cortical extract was increased to 8 c.c. on February 10 and 11. The condition improved, and except for a tendency to pyrexia and a slight cough the patient appeared to have recovered. From February 12 onwards the dose of extract was again 4 c.c. daily. On February 25 there was an unexpected relapse with nausea, vomiting, pyrexia, and cough. On February 26 he expectorated thick green sputum. On the 28th he appeared drowsy and refused most of his food, vomiting some milk and water. On March 1 his general condition was very poor, the patient lying in a semi-collapsed state on his right side with his knees drawn up and almost completely covered by the bed-clothes. His orbits appeared very hollow and dark, and there was a general increase in the intensity of pigmentation. The pulse was feeble and rapid. The next day the drowsiness and vomiting continued. His mouth was very dry and the throat red. His skin was hot and dry. A rectal saline was returned, but 100 c.c. of 5 per cent. glucose in saline intravenously appeared to produce an improvement, the patient being sufficiently roused to talk to his friends. On March 3 he again lapsed into a comatose state with incontinence of urine and faeces. He died that day. Post-mortem Number 119.

The systolic blood-pressure had fallen to 90 mm. after the first days of the influenza infection and again fell to 80 mm. during the last few days of life. During the latter period there was a rapid increase of pigmentation. There was a 7 lb. loss of weight in the latter part of February during the period of relapse.

SUMMARY OF NECROPSY (*P.M.* 119/1931) BY W. W. WOODS

Patient 3. The necropsy (*P.M.* 119/1931) showed destruction by caseous, slightly calcareous tuberculosis of the whole of the suprarenal bodies except a few microscopic remnants both of cortex and medulla (combined weight 9.8 gm.) A calcified fibro-caseous area was present in the lower lobe of the left lung near the hilum. There were calcified glands in the cervical and mesenteric glands. There was also acute purulent bronchitis, subacute haematogenous nephritis, and signs of subacute septic-aemia.

Kidney. In the upper medulla and to a less extent in the cortex were scattered focal areas of infiltration with large and small lymphocytes, neutrophil, and eosinophil leucocytes and a few plasma cells. Most of these areas were very small, but there were a few of considerable size in the medulla. They usually surrounded a tubule which contained desquamated epithelium and neutrophil leucocytes. In the larger areas the tubules appeared to be completely disintegrated. Leucocytes were also present occasionally within ascending tubules of Henle at a distance from areas of infiltration. There were hyaline casts in ascending limbs and, less often, in descending limbs of the loops of Henle. Throughout the kidney there were hyaline thrombi in glomerular capillaries, severe albuminous and dropsical degenerations of first convoluted tubules, conspicuous hyaline-droplet degeneration of first convoluted tubules, particularly of their straight portions, and isotropic fatty degeneration of ascending limbs of Henle and to a less degree of first convoluted tubules. In sections stained by Gram's method with neutral red no organisms were found except some groups of Gram-positive cocci and a few Gram-positive bacilli in one arcuate vein.

Case 4. J. B., a lad of 16 years of age, was admitted to the London Hospital on April 14, 1931. As a child he had been subject to 'bilious attacks'. Appendicectomy for acute appendicitis was performed in March 1927. At the age of 13 the boy stopped growing, and gave signs of lassitude and weakness. Thus, he would tire easily at school, and at home would often sit on a chair with his knees crossed and legs drawn up. In August 1930 it was noticed that he drank large quantities of water and passed much urine for some weeks. In September 1930 the colour of his skin became much darker, his lassitude increased, and he suffered from evening feverishness and nightmares. The latter, however, had been present to a less noticeable extent over a period of years. The diagnoses at this time were apparently jaundice and tuberculous glands. On October 20 the patient was seen by Dr. Saxby Willis who diagnosed Addison's disease and prescribed a course of hypodermic adrenalin injections, which produced a temporary improvement. Nevertheless, the patient remained weak, non-ambulatory, depressed, irritable, pigmented, and suffered from anorexia, nausea, and vomiting.

On admission to the London Hospital his general appearance was that of a slender boy of 13, his form being very frail, and his weight only 4 st. 7 lb. Diffuse pigmentation was present all over the skin with intensification at the usual sites, axillae, groins, anal cleft, extensor surface of forearms, knuckles of hands, outer surface of hips, extensor surface of knees and ankles. There was also pigmentation at the sites of the hypodermic injections. Marked pigmentation was present in the buccal mucous membrane and to a less extent on the gums and lips. The blood-pressure was 85 systolic, 50 diastolic. The heart, lungs, abdomen, and central nervous system appeared normal. His temperature was subnormal and his pulse rapid, 112. The urine, on admission, showed no abnormality. The Wassermann reaction was negative.

Course of events in hospital. Treatment was commenced on April 18, 1931, and consisted of 10 c.c. of cortical extract given intravenously every day except Saturday and Sunday. Occasionally the intramuscular route was substituted. On the third day of treatment the pigment appeared less and the patient's general condition better. On the fifth day he asked for and ate a large breakfast. Vomiting ceased with return of appetite. He was now able to sit up in bed without feeling giddy. At the end of a week he was able to get up on the couch, and at the end of two weeks he was able to wash himself and to walk short distances. This he had not been able to do for several months. The amount of work that he could do, as measured by an ergograph, was nearly double that performed on admission. He was much less pigmented and appeared to be making rapid progress. On May 7, however, there were signs of relapse, increasing lassitude, yawning, hiccups, and nausea. This coincided with an increase of blood-sugar and the onset of glycosuria. On May 12 he passed a large quantity of urine (3000 c.c.) and complained of a dry uncomfortable feeling in the nose and mouth, which had occurred in previous relapses during the last few months. On May 14 adrenalin (5 minims hypodermically twice a day) was substituted for cortical extract in view of the possibility of overdosage. No benefit was observed and on the 19th the cortical extract was resumed. On May 21 the patient was drowsy and fretful. His appearance was not unlike that seen in progeria, his countenance being very wizened. He had complete anorexia and vomited after any attempts to take food. His veins were now very collapsed, and with the needle in the lumen of the vein it

was not easy to withdraw blood, the vein collapsing down on the needle. There was considerable peeling of the skin, which remained remarkably light in colour. About this time he complained very much of aching of the knees which were constantly held in the flexed position. On May 22 he received 400 c.c. of saline intravenously with 25 c.c. of cortical extract, and later in the day 20 c.c. of extract intramuscularly. He was slightly better the next day, but very ill. On May 26 he was drowsy and irritable and very intolerant of any disturbance. He was passing only scanty quantities of urine. He felt the cold very keenly and needed multiple blankets and hot-water bottles. He would frequently screw his face up, half stretch himself, and ejaculate a cry of distress for which, however, he could give us no reason or explanation. On May 27 he was given 600 c.c. of saline intravenously, together with 50 c.c. of cortical extract, without any obvious benefit. Rothera's test for acetone was positive, but the ferric chloride test for aceto-acetic acid was negative. On May 28 five units of insulin were given, ten units on the morning of the 29th and five units in the evening. At midday of the 29th the blood-sugar had fallen from 0.25 to 0.15 per cent., but at midnight there was a severe hypoglycaemic reaction which was relieved by two lumps of sugar by mouth. In view of the apparently poor response to cortical extract, the complication of diabetes mellitus, and the patient's increasing intolerance to any injections, all treatment was then stopped (May 29). The patient's condition became worse. On June 2 he developed conjunctivitis in both eyes. He was conscious but collapsed, cold, and irritable. He refused all food and resented any interference. His temperature was subnormal, 96.4° F., his respiration moderately deep and not hurried, 22, and the pulse rapid and feeble 120. His colour was still relatively pale. He had complete anuria. The next day at 10 a.m. he became unconscious, with pupils dilated and fixed, and died at midday. The terminal clinical picture was more characteristic of Addison's disease than of diabetic coma.

SUMMARY OF NECROPSY (P.M. 260/1931) BY W. W. WOODS

Diabetes. Addison's disease. Atrophy and intralobular fibrosis of pancreas. Atrophy and infiltration of suprarenal bodies

Patient 4. Chronic haematogenous nephritis. Melanin pigmentation of skin and lips and, in areas, of dorsum of tongue, palate, cheeks, and kidneys. Subacute inflammatory infiltration of coeliac and lumbar and, to a slight degree, of axillary and cervical lymph glands. Central necroses in solitary follicles of small intestine. Slight albuminous degeneration of liver. Slight subacute inflammation of mucosa of pharynx, uvula, and dorsum of tongue. Incomplete development of testicles (each 2.5 × 1 × 1 cm.). Atrophy of heart. Slight healed endocarditis of mitral valve. Very slight fatty atheroma of aorta at its commencement and of common carotid arteries at their bifurcation. Slight oedema of lungs. Slight congestion of mucous membrane of stomach. Red marrow in sternum. Very wasted boy.

Weights. Body, 23.6 kg. (length 1.55 m.); heart, 106.3 gm.; kidneys, 255 gm.; spleen, 92 gm.; liver, 793.8 gm.; brain, 1545 gm.; right suprarenal body 0.75 gm.; left suprarenal body, 1.15 gm.; thyroid 14.8 gm.; thymus, 14.25 gm.; pituitary, 0.45 gm.; pancreas, 15.7 gm.; left testicle, 2.6 gm.

Macroscopic Examination

The suprarenal bodies were greatly reduced in size. The right measured 3.7 cm. long and 1.8 cm. broad and 0.15 cm. at thickest; the left $6 \times 1.1 \times 0.2$ cm. Their cortex was very thin and brownish red; the medulla was white and was relatively abundant in places.

The pancreas was reduced in breadth and thickness. It measured 15 cm. long and 1.8 cm. broad and 0.8 cm. at thickest. Its lobules were yellowish grey and were very small.

Microscopic Examination

The tissues were embedded in paraffin. Pieces of kidney and liver were cut upon the freezing microtome for the identification of fat.

Right suprarenal body. The capsule was thickened and was composed of dense fibrous tissue. In the site of the cortex was a narrow zone of greatly distended capillaries lying in a sparse, delicate connective tissue, which was infiltrated to a variable degree with lymphocytes, plasma cells, and histiocytes and a few eosinophil leucocytes. The infiltration was sometimes dense. Cortical cells were present only in a very few scattered groups of three or four cells. Their cytoplasm was homogeneous and most were much reduced in size. Their nuclei were often distorted and hyperchromatic or karyolytic, and were sometimes absent. The medulla was abundant throughout the greater part of the three sections. In a few places it was of normal appearance. Usually the parenchyma was reduced to a variable degree, whilst there was a corresponding separation of the delicate fibrils of the stroma and an infiltration with round cells similar to those in the cortex. With the increase of infiltration the cells of the parenchyma formed short columns and later gave place to small discrete cells and ultimately disappeared entirely.

Left suprarenal body. The atrophy of the gland was greater. In the cortex the interstitial tissue had become swollen, dense, and hyaline, and the capillaries were not distended. There were very few remaining cortical cells. In the medulla more parenchyma was present, but the atrophy and infiltration were greater than on the other side.

Pancreas. The lobules were greatly reduced in size. Throughout the greater part or the whole of each lobule the interstitial tissue was increased to a variable degree and was infiltrated with a few lymphocytes. The acini were all small, and the greater the fibrosis, the smaller the acini and the fewer, smaller, more rounded and more dissociated were their cells. Cells with deeply stained nuclei preponderate in the islands. The islands appeared to have been reduced in number, and almost all that remained were abnormally small. Many were surrounded by the fibrosis. The walls of their capillaries frequently showed variable degrees of hyaline swelling. Where this was most marked the island was represented by one or two small groups of cells separated by strands of hyaline fibrous tissue. In a very few larger islands all or almost all the cells had disappeared and the space was infiltrated with lymphocytes. There was no interlobular fibrosis.

Kidneys. In the cortex were numerous small anastomosing areas of fibrosis. In these areas spindle cells were usually scanty. They were frequently infiltrated with lymphocytes and a few plasma cells and eosinophil and neutrophil leucocytes. There was moderate atrophy of the included tubules, and these frequently contained bulky hyaline casts. The glomeruli showed none of the changes characteristic of Bright's disease. In the areas of

fibrosis the periglomerular tissue shared in the surrounding change and the glomeruli were sometimes shrunken. Beneath the capsule of the kidney were scattered completely hyaline and atrophied glomeruli. This did not appear to be the result of any chronic vascular inflammation or degeneration. Many of the afferent glomerular arterioles, attached to otherwise normal glomeruli, showed an acute non-fatty degeneration at the hilum. The lumen of these vessels was often filled with red corpuscles. In the upper part of the medulla there was a diffuse infiltration, and focal areas of denser infiltration, of the same character as that seen in the cortex. Occasionally the included tubules contained a few neutrophil leucocytes. There was albuminous degeneration of the first convoluted tubules. In the cells lining many of the tubules, particularly first and second convoluted, there was pigment which did not give the Prussian-blue reaction for iron and was bleached by hydrogen peroxide.

Liver. Slight albuminous degeneration of the hepatic cells and vacuolation of the nuclei of those nearer the portal systems.

Spleen. The pulp was infiltrated with numerous eosinophil leucocytes and large basophil mononuclear cells and phagocytes containing pigment which gave the Prussian-blue reaction for iron.

Upper cervical and axillary lymph glands. The centres of the secondary cortical nodules were pale and were composed of degenerated reticulum cells. A few of the sinuses were slightly distended by desquamated sinus cells.

Coeliac and lumbar lymph glands. Many of the sinuses were distended with desquamated sinus cells, and less numerous eosinophil leucocytes, lymphocytes, and plasma cells.

Lower ileum. A major part of the solitary follicles was occupied by secondary cortical nodules with very large pale centres.

Thymus. The cortex and medulla were well developed. The interlobular septa consisted of fibrous tissue.

Tongue. A few of the basal epithelial cells and a few spindle cells in the subepithelial tissue contained pigment which did not give the Prussian-blue reaction for iron and was bleached by hydrogen peroxide. A few phagocytes contained pigment which gave the Prussian-blue reaction.

Skin of neck. In the basal cells of the epidermis and in spindle cells of the dermis was much pigment which did not give the Prussian-blue reaction for iron and was bleached by hydrogen peroxide.

Thyroid gland. The interlobular septa were of normal thickness and structure. The acini did not vary greatly in size; they contained abundant colloid and were lined with sharply defined cubical or flattened cells. The interstitial tissue contained a few small areas of infiltration with lymphocytes.

Two parathyroid bodies were among the bodies selected as possibly being parathyroid. They contained very few oxyphil cells. One of them had a few acini containing colloid.

Testis. The seminiferous tubules were separated by much interstitial tissue in which no interstitial cells could be recognized. Few had a lumen, and some of them contained spermatocytes.

The *semilunar ganglion, cervical sympathetic ganglia, and pituitary and pineal glands* appeared normal.

Case 5. A. P., a female, aged 50, was admitted to the London Hospital on January 4, 1931. The first indication of disease was two and a half years previously when the skin became excessively pigmented following

exposure to the sun. The menopause occurred at this time. She nevertheless enjoyed good health until July 1930 when she began to tire easily and to lose her appetite. Her condition became progressively worse, and in October 1930 a combination of epigastric pain and nausea suggested to her medical adviser the possibility of gastric ulcer, and she was investigated from this point of view with negative results. She became bedridden and was seen in consultation in December 1930 by Dr. Adolph Abrahams, who made the diagnosis of Addison's disease, and kindly referred the patient for treatment with cortical extract.

While awaiting a supply of extract a modified Muirhead regimen was tried for three weeks; adrenalin α v of 1/1000 solution hypodermically twice a day and dried whole gland by mouth. There was no improvement, and on admission to hospital on January 4, 1931, the patient was very ill, collapsed, and wasted. Pigmentation was diffuse, but especially noticeable in the face, buccal mucous membrane, neck, shoulders, spinal prominences, axillae, groin, anus, vaginal mucous membrane, waist-line, elbows, knees, malleoli, dorsum of forearm, knuckles, anterior aspects of the legs; the palms of the hands had escaped, except for the lines of flexures, and there was a sharp transition to the pigmented forearm at the wrist; the soles of the feet were not pigmented. The heart-sounds were distant, pulse rapid (100) and weak. Systolic blood-pressure 90 mm. and diastolic 60. The temperature was subnormal, 97° F. The remainder of the examination was essentially negative including the Wassermann reaction. The patient was observed to stretch herself frequently and yawn, and also suffered from frequent attacks of hiccups. Occasionally she would screw her face up and utter involuntary cries as if in pain, which, however, she was not.

Course of events in hospital. Treatment was commenced on January 9 with 4 c.c. of cortical extract intramuscularly or intravenously twice a day. No improvement was observed during the next few days. The patient was very weak and vomited frequently. On January 14 bile was vomited several times throughout the day, and on examination the stomach appeared to be greatly dilated. In the evening there was unexplained pyrexia to 101° F. and delirium. The blood-pressure had fallen to 60/45, and there was considerable collapse. It was remarkable to observe that in spite of this exacerbation of the disease the pigmentation had definitely diminished since the beginning of treatment. On the morning of January 15 the patient was very collapsed, with feeble rapid pulse. She was quite lucid mentally, and complained of a dry mouth. Epigastric discomfort was eased by a mustard plaster. 600 c.c. of 5 per cent. glucose intravenously produced a very considerable improvement. The cortical extract during this period unfortunately contained very appreciable amounts of adrenalin, and its injection was sometimes followed by adrenalin reactions, such as palpitations and tremors. On January 17 a new supply of extract free from adrenalin was obtained, and the dosage increased to 6 c.c. twice a day, with a further increase to 10 c.c. twice a day on the 19th. On this date the clinical condition was again very poor, the systolic blood-pressure falling as low as 60. By January 22, however, there was a marked general improvement, and the blood-pressure rose to 85/50. Irritation of the skin was complained of at the time. The improvement continued for some days, vomiting ceasing, appetite improving, strength increasing, and pigment fading. The irritation of the skin was worse and there was some desquamation. There was a very considerable decrease in pigmentation, including that of a patch inside the mouth which had changed from black to deep

red. On January 29 and 30 there was considerable mental depression, and albuminuria was noticed for the first time. It was thought possible that the cresol preservative (0.3 per cent.) might be responsible for these, as also for the general pruritus, although no carboluria was present. The cortical extract was, however, stopped and adrenalin α viii of 1/1000 solution given hypodermically twice a day. The patient remained fairly well until February 4 when incipient relapse was suggested by inertia, hiccup, and nausea. The irritation of the skin was much less. Albuminuria persisted. Adrenalin injections were stopped and cortical extract free from preservative was given in 10 c.c. doses twice a day intravenously in the morning and intramuscularly at night. The blood-pressure was 80/50. The patient's condition improved slightly, but was not very satisfactory. The possibility of overdosage with cortical extract was considered and the quantities reduced to 10 c.c. a day. This change appeared to be followed by some improvement, and on March 4 the appetite was better and the patient stronger and able to sit up in bed. She continued in this relatively improved state and was sent home in an ambulance at her request on March 14.

The patient continued to receive intramuscular injections of cortical extract at her home. During the next few weeks she appeared better, but following a relapse a few minims of adrenalin were given in the afternoon as well as the cortical extract in the morning. She appeared to have developed a hypersensitivity to adrenalin, the latter being discontinued after two weeks. In the latter part of April she improved and sat out of bed for some hours each day. She was troubled with pains in the knees which had, however, occurred intermittently for the past two years. There was no rise in blood-pressure, 80/55. In May her condition was much the same, but in spite of the absence of any marked clinical improvement the pigmentation was hardly noticeable. Her face and conjunctivae were very pallid. On May 13 she was comfortable but rather sleepy. On the 14th she was very weak and vomited frequently. On the 15th she felt very ill at 4 a.m. She then slept until 7 a.m. when she awoke in a great heat with her face burning, but with a subnormal temperature. She was delirious, but after sleeping for another few hours awoke in a rational state although very nervous. In the evening she again experienced the sensation of heat but fell asleep. At 3.30 a.m. on May 16 she awoke feeling very queer and after a few minutes fell into unconsciousness, all signs of life being extinct by 5 a.m. There was no autopsy.

Case 6. B. G., a female, aged 43, was first seen by me on July 6, 1931, in a moribund delirious condition. Dr. T. Thompson kindly permitted me to attempt treatment with cortical extract, and to carry out investigations. The clinical details of the case are to be described in a separate publication by Dr. Thompson: only the essential facts will be briefly mentioned here. The history dated from June 1929. Menopause occurred some months previously. An exacerbation of weakness, vomiting, and pigmentation occurred a few weeks previous to admission to hospital. The clinical diagnosis of Addison's disease was certain—pigmentation was present inside the mouth and the blood-pressure was 70 mm. systolic, 50 diastolic. The Wassermann reaction was negative.

Treatment. On July 4 240 c.c. of 10 per cent. glucose in saline intravenously resulted in very transitory improvement; on the 6th, 600 c.c. of 5 per cent. glucose in saline, together with 50 c.c. of extract, were given

intravenously. About two hours later the patient had a rigor and became unconscious for an hour. On the 7th, 8th, and 9th, 10 c.c. of cortical extract were given intravenously night and morning; and subsequently 10 c.c. a day. On the evening of the 7th very slight improvement was indicated, the patient talking lucidly at intervals. The next day the clinical picture was quite different, the patient greeting me with a smile, and asking for breakfast. She was obviously much paler and the pigment continued to fade rapidly during the next few days. On the 4th day of treatment she ate eggs and bacon, which she had not been able to touch for some months. She got out of bed on July 21, and during the next few weeks helped to serve teas in the ward. On August 2 the extract was reduced to 5 c.c. subcutaneously daily, which dose the patient now receives at her home from the district nurse. When last seen on August 21, 1931, she appeared well, fairly strong, and happy. Details of blood-pressures and biochemical investigation are given in Fig. 1.

Summary of results of treatment with cortical extract. A brief preliminary report on five of the six cases has already been made. With patient 1 and 6, the effect of cortical extract was as definite and as dramatic as that of insulin in diabetic coma. In both cases the patient was almost moribund before treatment and within four days was sitting up in bed and asking for food. With patients 3 and 4 the initial result was equally definite, although not so rapid. Both were bedridden before treatment, but were able to walk within three weeks of first receiving cortical extract. With patient 2 the initial condition was not so grave, but the beneficial results of treatment were quite marked. With patient 5 there was intermittent improvement, but never any return to good health. The immediate results were therefore excellent in five cases out of six.

The late results were not quite so satisfactory. Thus, patient 3 died after an attack of influenza, which did not appear to be particularly severe. He was, however, only receiving very small doses of extract. As with insulin, it seems probable that the quantity of extract should be generously increased during an infection. Patient 4 developed the rare complication of diabetes mellitus and died. Patient 5 survived five months after treatment had commenced, a progressively severe anaemia being a complication. Three of the patients (1, 2, 6) are in good health up to the present time, that is two, six, and nine months after treatment was commenced. This latter group include the two patients (1, 6) who were almost moribund before treatment.

The Effect of Cortical Extract on the Symptoms and Signs of Addison's Disease

In cases that respond to treatment with cortical extract, nearly all the symptoms and signs of Addison's disease tend to disappear: asthenia, anorexia, nausea, retching, vomiting, hiccups, yawning, lethargy, wasting, photophobia, conjunctivitis, involuntary cries and facial grimaces, hypersensitivity to cold, irritability, negativism, pessimism, delirium, and, most striking of all, pigmentation. The latter needs more detailed consideration as do also blood-pressure, temperature, and biochemical changes.

Pigmentation. Within two or three days of treatment with cortical extract the decrease of pigmentation is sufficient to be spontaneously

commented upon by friends of the patient, as well as by trained observers. This improvement continues, so that after a month's treatment there may be a close approximation to normality. In no case, however, could it be said that all evidence of an abnormal degree of pigmentation had disappeared. The pigmentation of the mucous membrane is also affected, changing from a deep brown or black to a dull red.

Theoretically the changes in pigmentation may be due to dissolution, decreased deposition, or both. The rapid disappearance of pigment with large doses of extract suggests dissolution. The following observations are in favour of a decreased deposition. A mustard plaster applied to the skin before treatment, or with inadequate doses of extract, was followed within twenty-four to forty-eight hours by deep pigmentation. If applied during the second or third week of treatment, the subsequent local pigmentation was relatively inappreciable. Similarly in patients with initial small doses of extract, at the site of intramuscular injection there developed within twenty-four hours a pigmented spot about 0.5 cm. diameter with a central pale area. Latterly with larger doses such spots were not detectable. It is probable that both dissolution and deposition of pigment are affected by cortical extract.

Pigmentary changes usually run parallel to changes in the general condition, diminution occurring with improvement, and increase with relapse. This is true with or without treatment with cortical extract. There may, however, be no such correlation. Thus with patients 4 and 5 the decrease of pigmentation was not marked, even when the general condition was very poor. Patient 3 remained very pale until a few days before death. It is well recognized that pigmentation (cases 1, 5) may occur for several years before other symptoms, and that patients with acute Addison's disease may have little or no pigmentation.

An attempt was made to demonstrate the disappearance of pigment by biopsy examinations (patient 2) before, and eighteen days after, treatment. It was, however, impossible to compare absolutely identical sites. Dr. A. B. Bratton has kindly reported on the sections, as follows :

'Specimen taken on 5.2.31. Pigmentation of epithelium of skin from abdomen. Pigment iron-free by Perl's test.

The pigment was in fine granules of a rich dark-brown hue and was mainly situated in the deepest row of cells of the stratum Malpighii: the majority of these cells contained pigment, and for considerable distances none of them were pigment-free. The majority of the pigmented cells were scantiest opposite the summits of the wider papillae of the dermis. A few groups of cells in the more superficial layers of the stratum Malpighii were also pigmented. There was no pigment in the dermis.

Specimen taken on 23.2.31. The pigment appeared to be slightly less in amount than that present in the previous specimen; fewer cells were pigmented, and there was a greater proportion of cells containing only a few granules of pigment. The papillae in the section of the present specimen were, however, wider on the whole than those in that of the former, and pigment in both specimens was scanty in the basal layer of epidermis opposite

such wider papillae; this may have largely accounted for the difference in quantity of the pigment. The pigment in the specimen had a slightly less rich brown hue than that in the previous one.'

Cardiovascular system. Within the first week of treatment the heart-sounds became more distinct, the pulse stronger and less rapid. The changes in blood-pressure are less definite and call for detailed consideration. Most readings have been taken in these cases by a Tycos recording sphygmomanometer. The systolic pressures alone are here considered, the diastolic being proportionate but not obtainable with equal accuracy.

With patient 1, in spite of very dramatic clinical improvement, there was hardly any change of pressure (86 mm.) for a period of three weeks. Subsequently, without further cortical extract, there was a gradual rise to 120 mm. with occasional drops to 90 mm. during transitory relapses.

With patient 2, Fig. 2, there was no rise of blood-pressure (90 mm.) for thirty days although clinical improvement was definite. After this there was a rise to 110 mm. with a later drop to 96 mm., the patient continuing in good health.

With patient 3, Fig. 3, there appeared to be a slight fall in pressure, 90 to 80 mm., during the first week, despite the marked clinical improvement. In the fourth week there was a rise to 110 mm., which was inconsistently maintained for a few weeks, with a terminal fall to 85 mm. one day before death.

With patient 4 there was no change in pressure (85 mm.) coincident with clinical improvement but a fall to 70 mm. during the fatal relapse.

With patient 5, Fig. 5, the blood-pressure varied between 80 and 90 mm. except for periodic relapses when it would fall to 70 or even 60 mm. Clinical improvement was not a marked feature in this case.

With patient 6, Fig. 1, the first reading was obtained during a crisis, 70 mm., although another observer had obtained a reading of 86 mm. some days previously with a mercury sphygmomanometer. In spite of dramatic clinical improvement during the first few days there was no rise of pressure until the middle of the second week, 78 mm. There was then a gradual rise to 90 mm. in the third week, 100 mm. in the fourth week, 105 mm. in the sixth week, with a subsequent tendency to approach the lower level of 90 mm. The secondary drop bore some true relationship to a diminution of dosage.

The initial clinical improvement with cortical extract is not associated with an appreciable rise of blood-pressure. A belated rise usually occurs during the third week, but this may not be consistently maintained even with a satisfactory general condition. The upper limits of blood-pressure tend to be subnormal. Temporary or terminal relapses are associated with a fall of blood-pressure.

The delayed rise of blood-pressure following treatment with cortical extract would not appear to be a direct effect of cortical hormone, but more probably an expression of a readjusted metabolism.

In a limited number of experiments no rise of blood-pressure has been noted during a period of four hours after the intravenous or intramuscular injection of 10 c.c. of cortical extract, either in normal individuals, or primary hypotension, or Addison's disease. Records were taken every three minutes.

It is interesting to note that following suprarenalectomy in animals Swingle (40), Stewart and Rogoff (37), found that there was no fall in blood-pressure. Rogoff and Stewart (30) are inclined to regard the low blood-pressure in Addison's disease as a manifestation of intoxication, and not as an interference with epinephrine secretion. The fact that in some patients the pressure remains low in spite of marked clinical improvement, and the disappearance of any gross signs of intoxication, does not appear to support the intoxication theory. The potential role of adrenalin should not be too readily ignored; it will be discussed further in considering the significance of low blood-sugar.

Temperature. The temperature in Addison's disease tends to be sub-normal, and the patients are very sensitive to cold. They huddle under the bed-clothes, are very intolerant of open windows, and frequently complain that they are unable to get warm.

Treatment with cortical extract tends to the disappearance of these abnormal sensations, and the elevation of temperature to normal limits. Hourly records in patient 4 indicated an elevation of temperature within a few hours of injecting 10 c.c. cortical extract intravenously, although the amount of cortical extract required to produce this varied with the general condition. In the first week there was a latent period of two days following cortical extract therapy before the initial elevation of temperature occurred.

The basal metabolism (C. Brunton) in this patient was -5 before treatment and +3 one week after. Rowntree and Snell (35) found that the basal metabolism tends to be low in a crisis, and may then be increased by cortical extract.

Blood-sugar

In 1908 Bierry and Malloizel (4) pointed out that suprarenalectomy in dogs was followed by a fall in blood-sugar. This was confirmed by several observers, including Porges (26), Joelson and Schorr (19), Banting and Gairns (3), Swingle (40). Banting and Gairns (3), however, find that the low blood-sugar is only terminal or the result of shock from the operation. Stewart (39) finds that the blood-sugar is within normal limits until death, when a moderate diminution may occur. He believes that other observers worked with moribund animals.

Porges (26) was the first to point out that a low blood-sugar occurs in Addison's disease. In three cases he obtained the following values, 0.052, 0.033, 0.067 per cent.; using the gravimetric method of Pfluger-Allihn,

which gives normal values between 0.07 and 0.09 per cent. Similar findings were obtained by Rosenow and Jaguttis (32), who, however, do not regard a low blood-sugar as pathognomonic. Snell and Rowntree (35) summarize their findings thus: 'Hypoglycaemia, regarded by some German authors as a characteristic feature, has been present in a few of our cases as a terminal phenomenon. We agree with Rosenow and Jaguttis that it is not a pathognomonic sign nor even constant in its occurrence.'

In the present investigation blood-sugar estimations were carried out two or three times a week, 2 c.c. of blood being taken from the median basilic vein, and the method of Folin and Wu being used. Many of the tests were carried out before breakfast. This was not always possible or advisable, and some were done four hours after breakfast. The results corresponded, except in some instances when the latter specimens tended to be higher than fasting values. The results are best seen from the graphs (Figs. 1-5). Variations in normal individuals may be taken to lie between 0.08 and 0.10 per cent.

In Fig. 1, patient 6, it will be seen that the majority of blood-sugar values are below 0.07 per cent. and many are nearer 0.06 per cent., the lowest value being 0.05 per cent. Only one reading is above 0.08 per cent. There is perhaps a slight tendency to relatively high values in the third week of treatment with cortical extract, but this is followed by a fall to 0.06 per cent. level. The dose of extract was halved during the last few weeks.

In Fig. 2, patient 2, there is indicated a tendency to low blood-sugar values, although two readings are above 0.08 per cent.

In Fig. 3, patient 3, fasting blood-sugar values over a period of thirty days are all below 0.075 per cent. (The initial specimen was inadvertently taken after a glass of milk.) There is a tendency to rising values after three weeks treatment, and a terminal fall to 0.052 per cent. just before death. The trend of the blood-sugar curve in this case is not dissimilar to that of the blood-pressure curve.

In Fig. 4A, patient 4, the initial blood-sugar value is 0.052 per cent., and the three values during the first ten days are below 0.07 per cent. This case was then complicated by diabetes mellitus with the blood-sugar gradually rising to 0.36 per cent.

In Fig. 5, patient 5, the majority of the blood-sugar values over a period of ninety days are below 0.08 per cent., and three are as low as 0.062 per cent.

In patient 1 only a single blood-sugar reading was obtained, namely 0.071 per cent. This was on April 14, 1931, several months after treatment with cortical extract had been stopped.

The blood-sugar in six cases of Addison's disease was found to be almost constantly subnormal. Occasional normal values were obtained. These latter might be correlated with varying activity of the glands, or in some cases might be associated with delayed absorption of food (*vide infra*). The

administration of cortical extract for many weeks has little or no effect on the blood-sugar, but there may be a slight increase in the third week running parallel with a rise in blood-pressure. It has previously been reported (Levy Simpson (22)) that 10 c.c. of cortical extract intramuscularly or intravenously produced no appreciable change in blood-sugar during a period of observation, of three and a half hours in normal individuals, in Addison's disease and in diabetes mellitus.

The effect of adrenalin on the blood-sugar in Addison's disease. In a previous communication (Levy Simpson (22)) it was stated that adrenalin injections produced a rise of blood-sugar in Addison's disease. This, however, had apparently been shown previously by Forschback and Severin (11) and by Rosenow and Jaguttis (32), and a similar effect in suprarenalectomized dogs by Banting and Gairns (3).

Figs. 1 A, 2 A, 3 A show the effect of the subcutaneous injection of 10 minims of 1/1000 adrenalin in patients 6, 2, 3 respectively, blood-sugars and corresponding blood-pressures being recorded.

In patient 6 there was a rise of blood-sugar from 0.064 per cent. to 0.1 per cent. one hour after injection.

In patient 2 successive estimations during the first hour gave 0.07, 0.067, 0.068, 0.1 per cent. Although the tremors and subjective sensations were at a maximum within the first 5 minutes there was no rise of blood-sugar during the first 14 minutes. A similar phenomenon was observed with patient 5 in whom blood-sugars before and 8 minutes after adrenalin were 0.067 and 0.061 per cent. respectively. In patient 3, however, the blood-sugar had risen from 0.052 per cent. to 0.087 per cent. within 16 minutes, subsequent hourly readings being 0.092, 0.074, 0.062 per cent. In a repeated experiment with this patient readings before, 20, 40, and 80 minutes after were: 0.071, 0.11, 0.125, 0.133 per cent.

In three cases of Addison's disease, therefore, adrenalin injections produced a rise of blood-sugar from subnormal to normal.

Using two normal individuals as controls the following results were obtained after 10 minims adrenalin: before, 30, 60, 120 minutes later gave corresponding readings of 0.1, 0.132, 0.137, 0.1 per cent.; before, 10, 30, 60 minutes later gave corresponding readings of 0.087, 0.071, 0.105, 0.166 per cent. Thus the range of elevation of blood-sugar is similar to that occurring in Addison's disease, although the final values are higher in normal individuals.

The effect of 2 drachms of 1/1000 adrenalin by mouth was investigated in two normal individuals and two patients with Addison's disease. No rise of blood-sugar was observed. Two out of four patients with Addison's disease and one patient with idiopathic hypotension gave an apparent rise of 10 to 15 mm. of blood-pressure within 20 to 40 minutes. No rise of blood-sugar occurred.

Carbohydrate tolerance in Addison's disease. Eppinger, Falta, and Rudinger (10), in 1909, suggested that there was an increased carbohydrate

tolerance in Addison's disease. Their only evidence, however, was a failure to produce glycosuria by giving 300 grm. of glucose by mouth.

A carbohydrate tolerance test was carried out in three patients with Addison's disease, 50 grm. of glucose being given by mouth and blood-sugars being estimated at intervals.

Patient 2: before 0.11 per cent., 45 minutes 0.111 per cent., 90 minutes 0.074 per cent.

Patient 3: before 0.069 per cent., 45 minutes 0.08 per cent., 90 minutes 0.095 per cent.

Patient 6: before 0.08 per cent., 45 minutes 0.118 per cent., 90 minutes 0.123 per cent., 120 minutes 0.118 per cent.

These experiments suggest an increased carbohydrate tolerance, but there is also some indication of delayed absorption, which may complicate the results.

A further test on patient 2 was carried out several months later by E. N. Young of Victoria Infirmary, Glasgow. The patient was in good health and receiving 5 c.c. cortical extract daily. Before 0.106 per cent., 30 minutes 0.175 per cent., 60 minutes 0.143 per cent., 90 minutes 0.133 per cent., 120 minutes 0.118 per cent. These figures suggest a normal tolerance.

The significance of the low blood-sugar in Addison's disease. It has been suggested that the low blood-sugars found in Addison's disease (Levy Simpson (22)) may be due to an absence of adrenalin secretion, and that a continuous secretion of adrenalin in normal individuals may be a factor in the maintenance of the normal blood-sugar level. The frequency of the low blood-sugars are recorded in the previous sections, and the constant rise to normal values following adrenalin injections tends to support this hypothesis, as also does the fact that we are dealing with a diseased gland from the medullary portion of which adrenalin can be derived. Further, it has been shown (*vide supra*) that cortical extract produces no immediate rise in blood-sugar, and in some cases, at least, no ultimate rise in blood-sugar even in the presence of comparatively good health. If a belated rise of blood-sugar occurs with cortical extract therapy as is possibly shown by patients 3 and 6, a readjustment of metabolism rather than a direct effect of cortical extract is suggested. It would then appear that the frequently rejected idea of some relationship between cortical and medullary secretion is again raised for consideration.

That adrenalin is continuously secreted in health is not easy to prove. Cannon (6-8) has produced considerable evidence in support of his theory that adrenalin is secreted in various emotional conditions. Stewart and Rogoff (37) consider his evidence inconclusive. They, however, have shown that 'under ordinary experimental conditions adrenalin is liberated from the suprarenal glands at a constant rate'. They point out that this is not necessarily the case under normal conditions. Höglér (18) concludes from biological tests of the adrenalin content of venous and arterial blood in

man, that adrenalin is continually secreted in normal individuals, and that it is diminished or absent in Addison's disease. He therefore suggests that it may be a factor in regulating blood-sugar and blood-pressure. Oliver and Schäfer (24) in 1895 investigated the effects of dilute alcoholic and watery extracts of suprarenal glands which were extensively diseased (Addison's disease) and found that, in contrast to extracts from normal individuals, no effect was produced on injecting into the blood-vessels of dogs. They concluded that 'in advanced Addison's disease the physiologically active substance of the suprarenal capsule is no longer produced'.

The occurrence of diabetes mellitus with Addison's disease. The combination of diabetes mellitus with a pathological lesion of the suprarenals found at autopsy has been described in four cases by Ogle (23), West (45), Rabé (27), Montgomery (25). In three of these cases the suprarenal lesion was tuberculous, in one atrophy. In none of these cases was there any real evidence of Addison's disease in life. In two of the four cases haemochromatosis was present. In 1907 Heller (17) reviewed the literature of 800 cases of Addison's disease, and considered that in one case there was also evidence of diabetes mellitus. The evidence is too slight to be acceptable. Snell and Rowntree (36) describe a case of diabetes mellitus and exophthalmic goitre, in which symptoms of Addison's disease occurred as a terminal event. At autopsy marked atrophy of the pancreas and suprarenal glands was found. Arnett (2), 1927, described the first definite case of diabetes mellitus with characteristic symptoms of Addison's disease in life, and no other complication. At autopsy atrophy of the suprarenal glands was found. In a preliminary communication Allan (1), 1931, states that of 115 cases of Addison's disease and 3,000 cases of diabetes mellitus at the Mayo Clinic, there were two cases in which diabetes mellitus and Addison's disease occurred together. One of these was probably the one of Snell and Rowntree already quoted in which exophthalmic goitre was the presenting feature. The details of the second case are apparently to be published later.

Patient 4, in the present series, was a very definite case of Addison's disease in which diabetes mellitus developed during the last few weeks of life, and while under treatment with cortical extract. Numerous blood-sugar estimations were carried out and Fig. 4 A shows a gradual rise from the initial subnormal values to the terminal high value of 0.36 per cent. Glycosuria and ketonuria were present. Autopsy (*vide supra*) showed atrophy of the suprarenals and of the pancreas. There is a possibility that the effects of the pancreatic lesion were not obvious earlier owing to the inability to take food. On this supposition the improved appetite following cortical extract treatment revealed a latent defect. This patient showed a hypersensitivity to insulin, as was also found in the case described by Arnett (2), who refers to a similar hypersensitivity observed in suprarenalectomized animals by Sanberg, Hallian, and Gayet.

In spite of the rarity of diabetes mellitus as a complication of Addison's disease it is not necessarily a coincidence, and it is conceivable that the

hypothetical infection or toxin responsible for the so-called atrophy of the suprarenal glands is also responsible for the pancreatic lesion.

Blood Urea

The estimations were carried out by the Folin method with 1 c.c. of blood drawn from the median basilic vein. The values are fasting ones for the most part, but in view of the capricious appetites of the patients no attempt at a standard diet was possible.

In patient 1, whose treatment was carried out in a small house, only one blood-urea estimation was done, namely 0.027 per cent. on April 14, several months after treatment.

In patient 2, Fig. 2, blood urea was always within normal limits. The patient was never in crisis.

In patient 3, Fig. 3, the initial blood urea was high.

Although the patient was very weak on admission, he was not in crisis, and was taking a fair amount of fluids. There was a rapid fall of blood urea within the first week of treatment. During the influenzal infection and coincident clinical relapse, the blood urea remained within normal limits up to six days before death. Unfortunately the writer was himself indisposed at this period and no terminal blood-urea estimation was obtained.

In patient 4, Fig. 4, the initial blood urea, 0.064 per cent., was high for a lad of 16 years of age. It fell to 0.025 per cent. after two weeks' treatment with cortical extract. There was then a clinical relapse, and in spite of continued administration of cortical extract the blood urea gradually rose to the terminal figure of 0.17 per cent. Values as high as 0.075 per cent. were recorded within fifteen days of death. During this latter period there was a rapid decline in urinary excretion (Fig. 4), terminating in anuria. This case was complicated by diabetes mellitus, in coma from which high blood urea may occur. Nevertheless the blood urea in this case began to rise several weeks before coma supervened, whereas the increase in blood urea in diabetes mellitus does not usually occur until coma is present (Labbé and Boulin (20)). Further, the coma in this case resembled that of suprarenal inadequacy.

In patient 5, Fig. 5, the blood urea was initially high, 0.063 per cent., 0.079 per cent., and tended to fall to normal with cortical extract therapy. This, however, was not associated with marked clinical improvement, and a blood urea taken nine days before death was only 0.027 per cent. A severe anaemia was present in this case.

In patient 6, Fig. 1, the initial blood urea, with the patient semi-comatose, was very high, 0.1 per cent. There was a rapid fall within a few days of treatment with cortical extract to 0.06 per cent and then 0.02 per cent. It was maintained below 0.04 per cent. for some weeks and then there was a tendency to increase up to the level of 0.06 per cent., although the general condition remained very satisfactory.

The blood urea in comatose or semi-comatose phases of Addison's disease is high, and tends to return to normal with cortical extract injections. A high blood urea may be present apart from a crisis, but this is not usual. The blood urea is not a very reliable guide to the clinical condition.

Rowntree (33) found high blood ureas (about 50 mg.) in only two out of twelve cases, but also states (Snell and Rowntree (36)) that 'elevation of the blood urea is common, particularly in the terminal stages'.

The significance of a raised blood urea. Joelson and Schorr (19) found that in suprarenalectomized dogs there was increased blood urea, but this was associated with an increased concentration of blood. Stewart and Rogoff (38) found that in suprarenalectomized dogs 'no notable changes occur until shortly before death'. Working with cats, Hartmann and co-workers (13) found that the blood urea rises within the first three days to double, and remains there until just before death when it rises much higher. Swingle (40) found a marked decrease in the volume of urine passed just before death. Banting and Gairns (3), working with suprarenalectomized dogs, observed that 'the increase in urea and non-protein nitrogen seems to depend in some way upon the ability of the kidneys to excrete, since the administration of saline only reduced this when accompanied by diuresis'. In patient 4 large volumes of intravenous saline failed to produce diuresis or to reduce the blood urea.

It has been noted (*vide supra*) that in many cases of Addison's disease there is evidence, at least in the more severe phases, of impairment of renal function and of renal damage. Necropsies in patients 3 and 4 showed pathological changes in the kidneys. Hypothetical toxæmia from suprarenal inadequacy might be responsible for structural changes in the kidney. The latter might be accepted as the cause of the high blood urea, and urea retention. Another important consideration, however, is the dehydration, with resulting blood concentration. Probably both factors contribute. It is important to appreciate that an adequate clinical response to cortical extract is associated, within a few days, with the disappearance of evidence of impaired renal function.

Acute hypotension in crisis may influence urinary excretion, but it is certainly not the main factor, as the blood-pressure tends to remain low for two or more weeks after a return to normal function.

The problem of a raised blood urea in the severe phases of Addison's disease bears some analogy to that in intestinal obstruction and diabetic coma.

Urine

In patient 1 the urine contained a trace of albumin—no microscopic report.

In patient 2 the urine before and after treatment contained a cloud of albumin, hyaline or granular casts, epithelial cells, few leucocytes, and occasional red cells.

In patient 3 the urine contained a trace of albumin, no casts, occasional red cells. The urine was not examined during the last week of life.

In patient 4 there was no albumin during the first few weeks, but later albuminuria developed, and red cells and hyaline casts were found. The phenolsulphophthalein test one week before death showed a poor excretion, 14.8 per cent., and the urea percentage in the urine at that time being 0.63 per cent. Similar low figures for urinary urea had been obtained ten days previous to this, indicating a urea retention. This patient also developed glycosuria and ketosis.

In patient 5 the urine was initially free from albumin and of approximately normal specific gravity 1020. In the third week albuminuria was found, and the subsequent specific gravity was maintained fairly constantly at 1010 and indicated impaired renal function. There were red cells but no casts.

In case 6 the urine contained a cloud of albumin, few red cells and leucocytes, but no casts, on the fourth day and again in the fifth week of treatment.

All the urines contained albumin and a few red blood-cells. Three out of six showed casts. Definite evidence of impaired renal function was present in at least two cases, of which one showed indications months before death. Snell and Rowntree (36) state that urine analysis and renal functional tests almost invariably show evidences of renal involvement.

Urinary Creatine and Creatinine

Dr. R. H. Dobbs kindly undertook an investigation of the creatine and creatinine urinary content in patient no. 4, and of the variations produced by cortical extract therapy. His report is appended below. There appears to be a fall in the ratio of creatine to creatinine following cortical extract administration. The possibility of this serving as an indication for dosage will be explored further.

'At the suggestion of Dr. Levy Simpson, I made observations on the creatinine and creatine excretion of this patient. Estimations were made daily on a twenty-four hourly specimen of urine by Folin's method, a standard creatinine solution being used for colorimetric comparison, and the conversion of creatine to creatinine being effected by autoclaving for twenty minutes at 120° C. No attempt was made to regulate the patient's protein intake, which intake did in fact vary within wide limits.

The results are tabulated in Table I. The fourth column representing the creatine : creatinine ratio. This has been chosen because of its independence of faulty collections of urine, difficult to avoid in a young, very ill, sometimes incontinent patient.

The table shows a creatinine excretion lower than should be found in a healthy male aged 16 years, and a degree of creatinuria that is pathological for this age. During the first eighteen days of treatment with

suprarenal cortical extract, there was an increased creatinine excretion with a decrease in the creatinuria, producing a marked fall in the creatine: creatinine ratio. One noticeable check in this fall occurred after the first of two days during which extract was not given. The fall followed twenty-four hours after the first injection of the extract, and anticipated clinical improvement by some days. A subsequent rising and fluctuating ratio occurred twenty-four hours after extract was again withheld for two days, and six days before a clinical relapse. The latter was associated with signs of renal insufficiency and diabetes mellitus, with marked ketonuria, and these may be factors in producing the irregularity in the ratio after May 2.

TABLE I

Date.	Quantity of urine c.c.	Mg. of creatinine.	Mg. of creatine (as creatinine).	C/Cn.	Treatment with cortical extract c.c.	Date.	Quantity of urine c.c.	Mg. of creatinine.	Mg. of creatine (as creatinine).	C/Cn.	Treatment with cortical extract c.c.
April 16	525	321	336	0.105	—	May 11	1135	355	323	0.91	10
17	590	215	215	1	—	12	2100	689	563	0.82	10
18	990	320	320	1	10	13	1680	694	406	0.59	10
19	782	326	272	0.84	10	14	800	345	222	0.65	adren- alin
20	917	367	313	0.85	10	15	1485	530	392	0.74	"
21	1040	425	318	0.75	10	16	1600	485	241	0.5	"
22	1025	427	305	0.72	10	17	940	373	187	0.51	"
23	1040	397	273	0.69	10	18	520	346	122	0.35	"
24	680	414.5	166.5	0.4	10	19	1355	307	188	0.62	10
25	1080	469.5	158.5	0.33	—	20	325	183	63	0.34	10
26	780	338.5	190	0.56	—	21	565	404	302	0.75	10
27	1233	537	211	0.39	10	22	735	350	280	0.78	45
28	926	386	159	0.41	10	23	810	368	201	0.55	20
29	1197	508	239	0.47	10	24	540	338	131	0.39	20
30	1190	575	203	0.35	10	25	305	231	104	0.45	—
May 1	845	321	109.5	0.34	10	26	415	275	94	0.33	—
2	1300	491	131	0.27	—	27	710	417	228	0.55	50
3	1170	432	181	0.42	—	28	285	380	163	0.33	—
4	1208	403	207	0.52	10	29	Urine lost				—
5	1035	450	413	0.92	10	30	340	232	116	0.49	—
6	1365	506	222	0.64	10	31	245	153	111	0.73	—
7	1643	823	525	0.64	10	June 1	225	187	128	0.68	—
8	1400	486	447	0.92	10	2	No urine passed				—
9	1863*	385	338	0.89	—	3	"	"	"		—
10											

* The urines for these two days were inadvertently mixed.

Creatinuria has been found in many diseases including the muscular dystrophies [A. Hunter, *Monograph*, 1928], and it is probable that the creatinuria and the lowered creatinine excretion are due to the muscle wasting in this case of Addison's disease. A few estimations on two other cases tended to give similar results, though the data were insufficient to show a definite response to administration of cortical extract.

Inorganic Phosphates

The values for plasma inorganic phosphates varied between 2.75 and 5.5 mg. per cent. In patient 4 the values tended to be slightly raised, 5.0, 5.0, 5.25, 5.0, 5.3. Swingle (40) found that in suprarenalectomized cats the serum phosphorus was high in the pre-coma stage, 5.9 to 16.3 mg. per cent. This might be due to impaired renal function.

Blood Cholesterol

Joelson and Schorr (19) found an increase in blood cholesterol in three out of four suprarenalectomized dogs. Swingle (40), working with cats, found no change. Snell and Rowntree (36) found 'slight and inconstant changes' in Addison's disease. Mr. J. R. Marrack obtained the following figures in four patients of this series: patient (2), 0.10 per cent.; patient (3), 0.15 per cent.; patient (4), 0.04 per cent.; patient (5), 0.19 per cent., 0.15 per cent., 0.06 per cent.

Test Meal

The Ewald test meal was used in three cases (2, 3, 5). Free hydrochloric acid was absent in all three, and the total acidity was low, 14, 25, and 17. A fractional test meal in patient 3, however, showed a slight amount of free hydrochloric acid from 45 to 75 minutes after the test meal. There were also traces of pepsin during this limited period. In patients 2 and 5 the tests were done before treatment; in patient 3, some weeks after treatment with cortical extract, the patient feeling well. A fractional test meal in patient 6 had to be interrupted owing to nausea, but some fractions showed free hydrochloric acid to be present within normal limits. This test was carried out some weeks after treatment with cortical extract commenced, and with the patient in excellent condition.

The Blood Count in Addison's Disease

A detailed report on the blood counts is given in Table II. In patient 1 the estimation was carried out by Dr. A. Greenwood of Maidstone, and the first blood count in patient 5 by Dr. C. R. Lane at Hampstead Hospital. Apart from these two estimations, all blood counts were carried out in the Hale Clinical Laboratory under the supervision of the Director, Dr. P. N. Pantou.

In cases 1, 2, 6 there was no anaemia. In cases 3, 4 there was a slight secondary anaemia. In case 5 there was no initial anaemia, but a very severe and progressive secondary anaemia developed while the patient was under treatment. In this case one cannot exclude absolutely the possible effect of cresol preservative, 0.3 per cent., used in the cortical extract from

January 9 to 30. This was probably not the cause of the anaemia, however, as no such effect from cresol was seen in patients 2 and 3, treated about the same time, and no carboluria was present. The history, clinical condition, and course of events did not give any indication of neoplasm, nor at any time was there any evidence of pernicious anaemia. The cause of the severe secondary anaemia in this case remains unsolved. Rowntree (33) found definite anaemia to be present in one case in a series of forty-seven cases.

TABLE II

	Case No.	Date.	Treatment.	Erythrocytes (millions per cubic mm.).	Haemoglobin %.	Colour Index.	Leucocytes (per cubic mm.).	Neutrophils %.	Eosinophils %.	Small lymphocytes %.	Large lymphocytes %.	Large hyaline %.
17.12.30	1	28.11.30	C	?	70	?	4900	50	6	38	?	6
	1	17.12.30	C	5.3	70	0.65	8600	51	3	25	16	5
	2	3. 1.31	Nil	4.5	74	0.82	6800	62.5	0.5	24	5	8
	2	13. 3.31	C	4.9	72	0.71	3200	42.5	2	38	12	5
	3	30.12.30	A	4.1	58	0.70	8000	29	7	50	10	4
	3	9. 1.31	C	4	50	0.62	8800	49.5	4.5	38	4	4
	3	3. 2.31	C	4.2	64	0.77	6000	35	5.5	44.5	10	5
	4	15. 4.31	A	4.2	60	0.71	5600	40	5	39.5	9.5	6
	4	21. 5.31	C	4.5	58	0.64	7200	70	1	25.5	8	5
	4	2. 6.31	C	3.8	55	0.72	9000	50.5	6.5	35	4	4
	5	11.12.30	Nil	4.9	83	0.83	3600	47.5	8	36	?	8
	5	4. 1.31	A	4.2	63	0.75	5000	54	4.5	26	6.5	8.5
	5	29. 1.31	C	3.5	36	0.51	7000	57	6	24	10	3
	5	13. 2.31	C	3.1	40	0.64	5000	59	5	23	6	5.5
	5	7. 3.31	C	2.2	30	0.68	5600	60.5	5.5	21	9.5	3.5
	6	29. 6.31	C	5	75	0.75	6200	49.5	3	32	8	7
	6	24. 7.31	C	4.3	64	0.74	7000	42.5	5.5	29	19.5	3.5
	6	10. 8.31	C	4.6	68	0.73	6800	47.5	4.5	22.5	15	9.5

C = cortical extract.

A = adrenalin.

A slight but definite eosinophilia was seen in all but the second case. Eosinophilia may be present after various forms of organotherapy, such as liver, insulin, &c., but it will be seen from Table II that eosinophilia in Addison's disease occurs quite apart from treatment. Dr. P. N. Pantou has suggested that the skin pigmentation may be a factor, as eosinophilia is common in various skin lesions. The pigmentation in Addison's disease may be associated with desquamation.

The differential white cell count in many of the blood counts (Table II) shows a diminution in the number of polymorphonuclear neutrophils and a relative lymphocytosis. This, as well as mild eosinophilia, has also been noted by Rowntree and Snell (35).

Radiology in the Diagnosis of Addison's Disease

In 1914 Rolleston and Boyd (31 a) described shadows in the suprarenal area on radiological examination of a patient with Addison's disease. Rowntree and Snell (35) report similar findings in about a third of their cases. Thompson (44) records positive radiological findings in one case. Dr. M. H. Jupe has examined four of the present series and his report is appended below. Positive radiological evidence of calcification of the suprarenal gland was obtained in three out of four patients. The one with negative findings, patient 4, showed only atrophy of the suprarenals at autopsy. Patient 3 showed calcification of the suprarenals at autopsy, thus confirming the radiological findings. Patient 2 was examined radiologically at another hospital, and some evidence of calcification of the suprarenals was reported. The radiological findings in patient 6 were apparently negative.

The Role of Adrenalin in the Treatment of Addison's Disease

As a therapeutic measure the hypodermic injection of adrenalin together with dried gland by mouth has been used for some years at the Mayo Clinic with encouraging but variable results (Snell and Rowntree (36)).

In the present series of cases, patients 1, 3, 4, and 5 received this treatment for some weeks before the injections of cortical extract. Although transient improvement sometimes occurred, in no case was this sustained, and the patients were very ill at the time cortical extract was commenced.

The injection of adrenalin may cause severe reactions, and it should never be given intravenously. The hypodermic injection of minims 10 of 1/1000 solution almost invariably causes unpleasant symptoms, and in some patients even 3 minims may do so. This is true also with normal individuals. In Addison's disease the sensitivity to adrenalin varies with the phase of the illness, even with the same individual.

The reaction occurs within a few minutes of injection, is at its maximum for five minutes or more, and may persist to a slight extent for half an hour. When severe it is characterized by tremors of the limbs, the lips, and the trunk muscles. The tremor is most noticeable on moving the arms, or, in the case of the lips, when talking. There is a coincident pallor of the face, especially the tip of the nose. The pulse becomes rapid and feeble, and may cease to be palpable at the wrist. There may be a feeling of constriction of the chest with difficulty in breathing, or with shallow respirations. The nails of the hands may take on a cyanotic tinge. The pupils may dilate.

In one patient a sudden pain in the left side was felt within two minutes of injection. The pain persisted for forty-eight hours, was worse on breathing, and was associated with pyrexia of 103° F. The condition suggested pleurisy, possibly from a small pulmonary embolus, but no friction rub was detected. With 3 minims of 1/1000 adrenalin, one patient became confused and

disorientated. This recurred on successive days, and the patient found it advisable to remain quite still and not talk for thirty minutes after each injection. In some cases there is fear of imminent death, and reassurance is necessary. The reaction may leave the patient in a weak and collapsed state.

Intravenous Saline and Glucose in the Treatment of Addison's Disease

Several physiologists have commented upon the fact that intravenous salines, with or without glucose, prolong the life of suprarenalectomized animals (Banting and Gairns (3), Hartmann (15), Rogoff and Stewart (29), Swingle (40)). It was used as a counter measure to the increasing concentration of the blood that follows suprarenalectomy. Banting and Gairns (3) also point out that the serum of suprarenalectomized dogs is toxic, producing diarrhoea and vomiting when injected into other dogs. Fluid dilutes the toxins. Glucose was added to the saline because of the low blood-sugar, and the inability of the animals to assimilate nourishment. The chief value of the procedure is, however, the administration of fluids, which should be given repeatedly and in large quantities. The dehydration of patients in the crises of Addison's disease has already been commented upon, and it is in this phase of the disease that intravenous salines, with or without glucose, are of some value. Snell and Rowntree (36) have found it useful. It was employed in five of the present series of cases.

In patient 1, 600 c.c. of intravenous glucose given before cortical extract was commenced resulted in transitory improvement. In patient 3 a similar procedure led to the appearance of remission, but death occurred the next day. In patient 4, 600 c.c. of intravenous saline was given twice during the last ten days of life with little benefit. In patient 5, 600 c.c. of intravenous saline with glucose, given during the first week in hospital, resulted in the patient rallying from a critical state. In patient 6, 240 c.c. of intravenous saline with glucose produced a few hours' improvement; two days later 600 c.c. were given with the addition of 50 c.c. of cortical extract, the patient making a dramatic recovery from a semi-comatose state.

Intravenous saline, with or without glucose, is therefore of benefit in the crises of Addison's disease, but little should be expected from this procedure alone. It is an accessory part of the treatment, its use being comparable to that of intravenous saline in diabetic coma.

Summary

1. Six cases of Addison's disease, and their treatment with cortical extract, are described.
2. All benefited from cortical extract therapy, but three subsequently died. Complications were present in these three cases, namely influenza, diabetes mellitus, severe anaemia. The three surviving patients are in relatively good health, although two of these were almost moribund at the time treatment was initiated.

3. A fairly persistent low blood-sugar is noted to occur in Addison's disease, and the effect of adrenalin in raising it is recorded. The possibility of adrenalin being a factor in regulating blood-sugar is discussed. Carbohydrate-tolerance tests give some indication of increased tolerance in Addison's disease, but the probability of delayed absorption is a complicating factor.

4. A case of diabetes mellitus coexisting with Addison's disease is described.

5. High blood urea occurs in severe phases of Addison's disease, together with urea retention and impaired renal function. Renal damage and dehydration are considered to be important factors. The significance of creatine and creatinine variations are discussed.

6. A low gastric acidity or complete achlorhydria is frequently met with in Addison's disease.

7. Blood counts show a moderate eosinophilia, and a relative lymphocytosis. Marked anaemia is not usually a feature of Addison's disease, but may occur.

8. The value of radiology in confirming the diagnosis of Addison's disease is illustrated.

9. Details of treatment with, and dosage of, cortical extract are discussed; also the subsidiary role of intravenous fluids and adrenalin.

It is with much pleasure that I acknowledge the advice and help of Dr. J. R. Marrack, Clinical Pathologist to the London Hospital; also of Dr. P. N. Panton, Director of the Hale Clinical Laboratories; Dr. W. W. Woods, Assistant Director of the Bernard Baron Institute of Pathology; Dr. R. A. Rowlands, Dr. O. Leyton, and Dr. T. Thompson, Physicians of the London Hospital; especially am I indebted to my Chief, Dr. Robert Hutchison, without whose guidance and co-operation this investigation would not have been possible.

Messrs. Allen and Hanburys have given free supplies of cortical extract for experimental purposes, and their scientific staff have showed much keenness and skill in facilitating this work.

I wish to express my thanks to Dr. Marrack for permission to work in the Clinical Laboratory and for his help in carrying out these investigations.
R.H.D.'

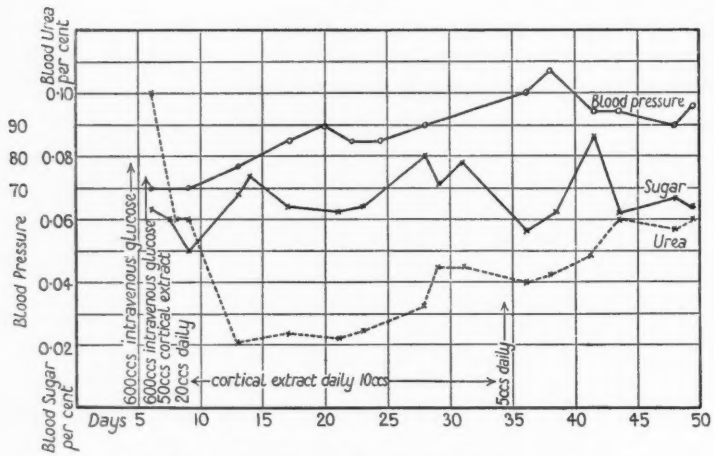


FIG. 1 (Case 6). Treatment with Cortical Extract.

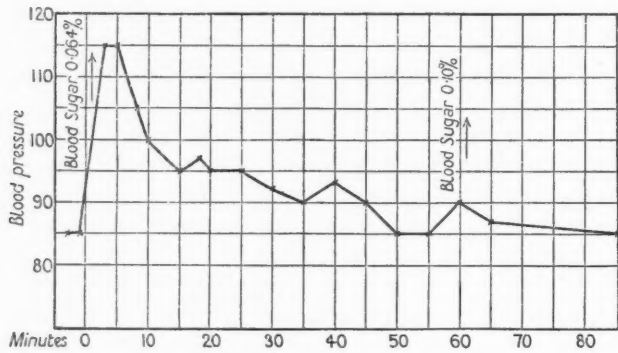


FIG. 1A (Case 6). Effect of Adrenalin.

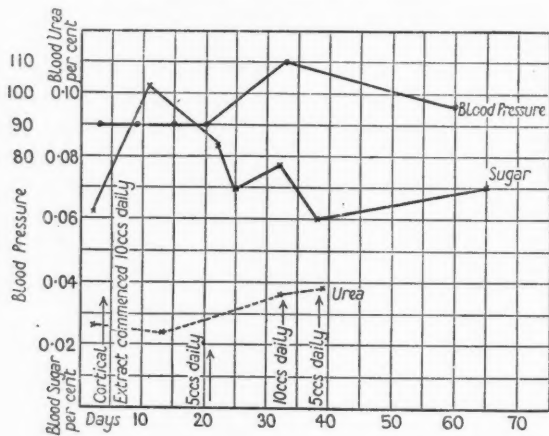


FIG. 2 (Case 2). Treatment with Cortical Extract.

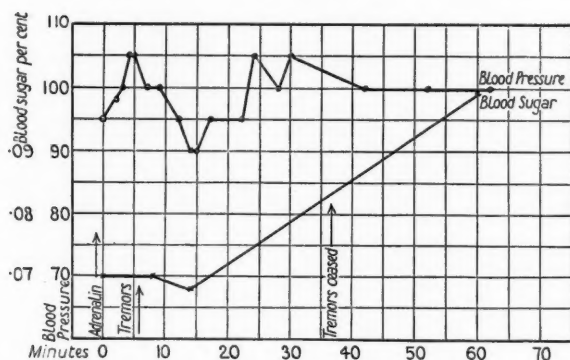


FIG. 2A (Case 2). Effect of Adrenalin.

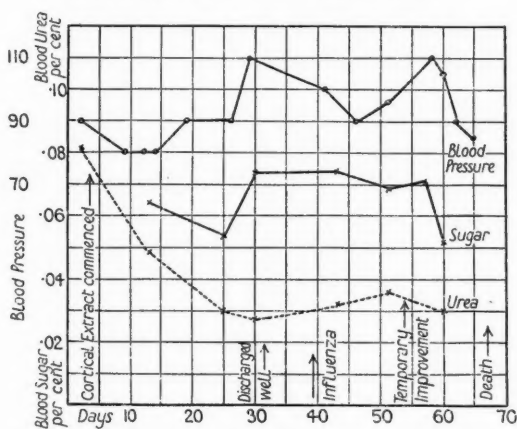


FIG. 3 (Case 3). Treatment with Cortical Extract.

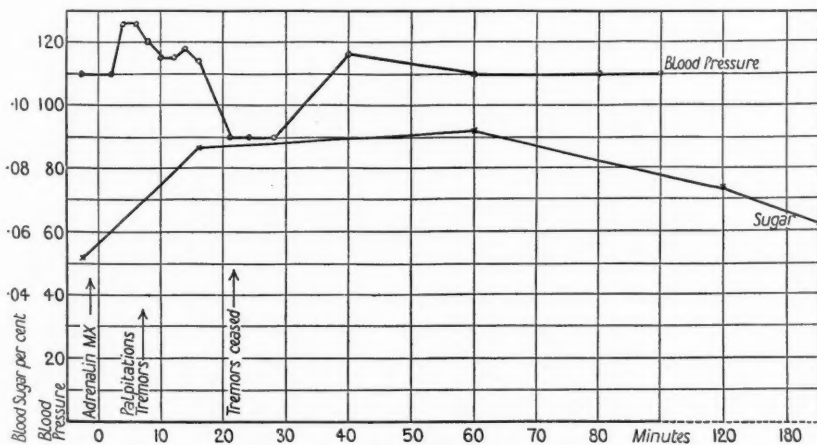


FIG. 3A (Case 3). Effect of Adrenalin.

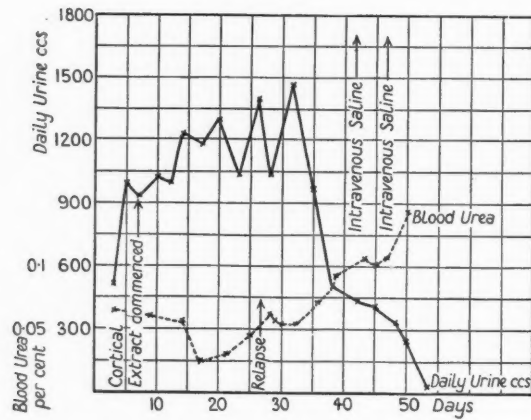


FIG. 4 (Case 4). Failure of Renal Function.

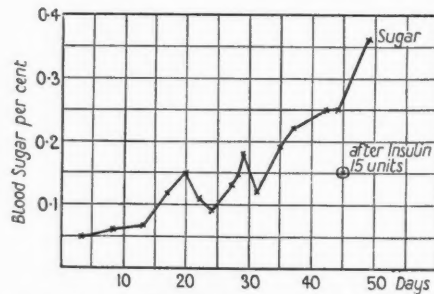


FIG. 4A (Case 4). Development of Diabetes Mellitus.

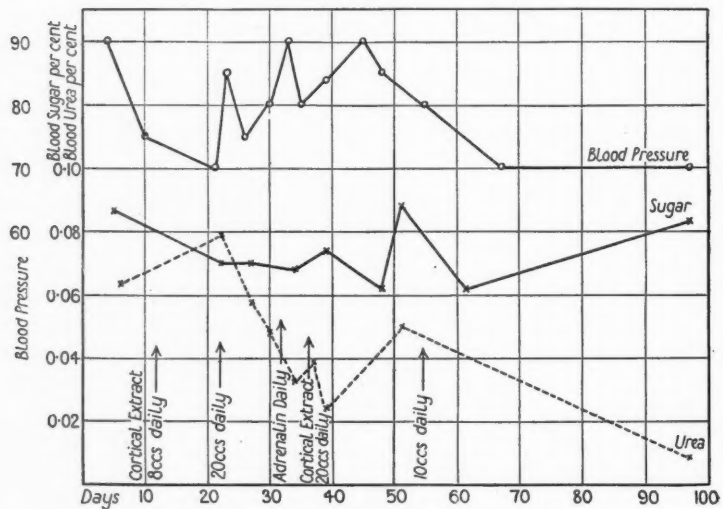


FIG. 5 (Case 5). Treatment with Cortical Extract.

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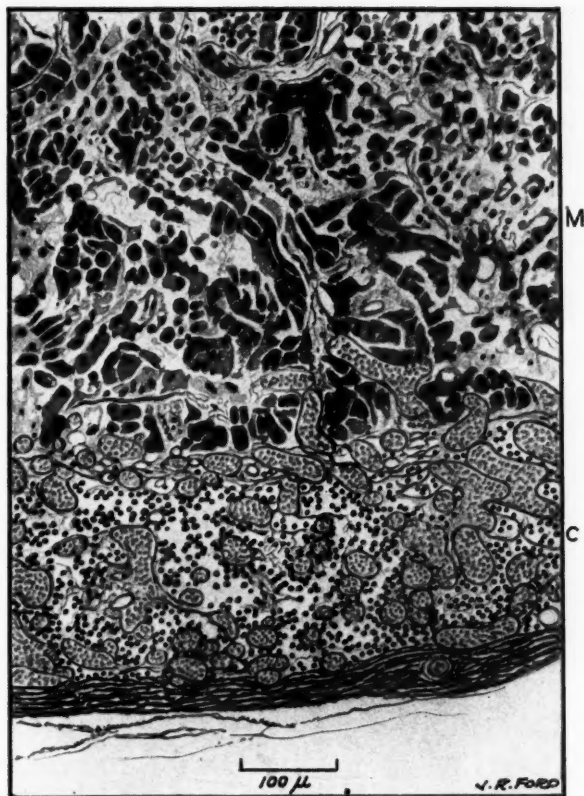
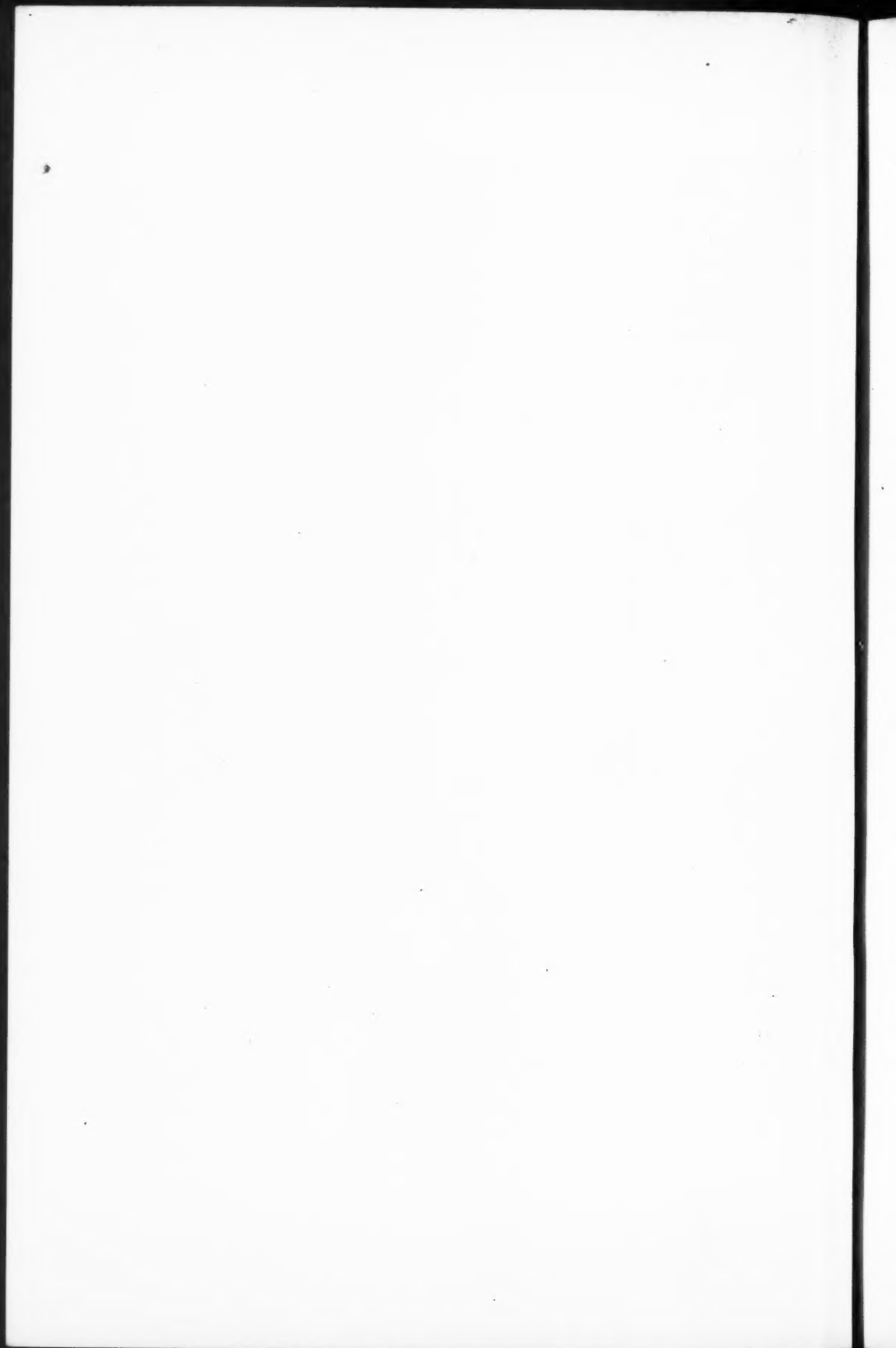


FIG. 6. Right suprarenal body. Weigert's iron-haematoxylin and van Gieson. Engorgement of completely atrophied and infiltrated cortex (c); infiltration and considerable atrophy of medulla (m)



FIG. 7. To show calcification of the affected adrenal



ON THE OCCURRENCE OF COPPER AND MANGANESE IN PREPARATIONS OF IRON¹

By J. H. SHELDON AND HUGH RAMAGE

(From the Royal Hospital, Wolverhampton)

THE work of Waddell, Elvehjem, Steenbock, and Hart (1) has shown that preparations of carefully purified iron are ineffective in the treatment of nutritional anaemia in rats. If, however, traces of copper are supplied in addition, the haemoglobin is rapidly regenerated, and these workers find that other metals are incapable of replacing copper in this function (2). Titus, Cave, and Hughes (3) and Mitchell and Miller (4) state, however, that copper is not alone in being a necessary adjuvant to the formation of haemoglobin, and consider that there is a group of elements which is active in this respect, manganese being one of these.

These facts suggest that the efficacy of the large doses of iron nowadays employed in the treatment of anaemia may be due in part to the presence of other metallic impurities, especially as the amount of iron commonly given is out of all proportion to the amount actually required for the regeneration of haemoglobin. The blood of a healthy adult contains about 40 gr. of iron, while the dosage of iron recommended by Witts (5) in the treatment of chronic microcytic anaemia is from 60 to 120 gr. of iron and ammonium citrate daily over a period of at least three months. The total iron intake (reckoned as the metal) will be from 1,100 to 2,200 gr., which seems excessive to cure a total deficiency of less than 40 gr.

It is worthy of note that the preparations of iron and ammonium citrate used by Mackay in her work on the nutritional anaemia of infants (6) contained traces of both copper and manganese, while Elvehjem and Lindow (7) analysed ten iron salts, and found traces of copper in eight, in amounts varying between 0.008 and 0.04 mg. per 1 grm. of sample.

It therefore seemed desirable to investigate a series of preparations of iron in order to ascertain the regularity with which these impurities might be found. Sixty-five samples of iron preparations in common use in medicine were taken from different sources. Some were obtained direct from the Hospital Dispensary, others were supplied by British Drug Houses, Ltd., and by Messrs. Burroughs and Wellcome, Ltd. (In the tabulated results no reference is made to the firm supplying the drug.)

¹ Received September 10, 1931.

They were investigated spectroscopically by the method described by one of us (H. R.) (8)—weighed amounts (0.02 grm.) being burnt in an oxy-coal-gas flame before the slit of a quartz spectrograph. Quantitative results were obtained by comparing the lines so obtained with those derived from the burning of varying amounts of standard solution. The flame spectrum, while giving lines due to copper and manganese that are easily recognizable when only the merest traces are present, is much less sensitive in the detection of zinc, and the absence of any reference to this element is not to be regarded as necessarily indicating its absence from the specimens examined.

The lines given by the weakest strength of the standard solution employed in this investigation represent 0.005 per cent. of copper and 0.002 per cent. of manganese. When the lines in question are weaker than this, a 'trace' has been said to be present. The strongest strength of standard solution gave lines representing 0.05 per cent. of copper and 0.02 per cent. of manganese, and amounts above this are indicated by the sign +.

TABLE I (— indicates absence)

No.	Drug.		Copper.	Manganese.	Remarks.
1	Ferri pyrophosphas	(a)	Trace	0.002 %	
2	" "	(b)	—	Trace	
3	Ferri et quininae citras	(a)	0.018 %	0.005 %	Trace of lead
4	" "	(b)	Trace	0.02 %	
5	" "	(c)	0.005 %	0.01 %	
6	Ferri et quininae citras cum strychnina		—	0.005 %	
7	Ferri et quininae citras cum cinchonidin		Trace	0.01 %	
8	Ferri et ammonii citras	(a)	Merest trace	0.005 %	
9	" " "	(b)	Merest trace	0.01 %	Trace of lead
10	" " "	(c)	Merest trace	0.02 %	
11	" " "	(d)	—	Trace	Trace of lead
12	Ferrum redactum	(a)	0.005 %	+ 0.02 %	
13	" "	(b)	Merest trace	0.0075 %	
14	" "	(c)	0.025 %	+ 0.02 %	Manganese line very strong
15	Ferri perchloridum	(a)	Trace	+ 0.02 %	Lead 0.125 %
16	" "	(b)	0.005 %	+ 0.02 %	Trace of lead. Manganese line very strong
17	Liquor ferri perchloridi		0.003 %	+ 0.02 %	
18	Tinctura ferri perchloridi		Trace	0.005 %	
19	Ferri sulphas	(a)	Trace	0.005 %	
20	" " (exsicc.)	(b)	0.005 %	0.002 %	
21	" " (pure)	(c)	Merest trace	Trace	
22	" " (exsicc.)	(d)	Merest trace	0.01 %	
23	" " (commercial)	(e)	Merest trace	0.002 %	
24	Ferri valerianas	(a)	Merest trace	Merest trace	
25	" "	(b)	Merest trace	Merest trace	
26	Easton's syrup (tabloid)	(a)	Trace	0.005 %	
27	" " (fluid)	(b)	Merest trace	Trace	
28	" " (tabloid)	(c)	Trace	0.003 %	
29	Syrupus ferri phosphatis compositus		Merest trace	Trace	
30	Syrupus ferri iodidi		Merest trace	0.005 %	

COPPER AND MANGANESE IN PREPARATIONS OF IRON 137

TABLE I (*continued*)

No.	Drug.	Copper.	Manganese.	Remarks.
31	Ferri iodidum	0.05 %	+ 0.02 %	Manganese line very strong
32	Compound syrup of hypo-phosphites	—	+ 0.02 %	Manganese line very strong
33	Ferri hypophosphas	—	Trace	
34	Ferri lactophosphas	Merest trace	0.002 %	
35	Ferri glycerophosphas (a)	—	Merest trace	
36	" " (b)	Merest trace	Merest trace	
37	Ferri et strychninae phosphas	Merest trace	Merest trace	
38	Ferri phosphas saccharatus	Merest trace	Merest trace	
39	Ferrum (no. 35 wire)	Merest trace	+ 0.02 %	Manganese line very strong
40	Ferri carbonas saccharatus (a)	0.0125 %	0.02 %	
41	" " " (b)	—	0.02 %	
42	Ferri et potassii tartras	0.005 %	0.005 %	
43	Ferri bromidum	Merest trace	+ 0.02 %	Manganese line very strong
44	Ferri arsenas (a)	Merest trace	0.009 %	
45	" " (b)	Trace	Merest trace	
46	Ferri oxalis	Merest trace	+ 0.02 %	Manganese line very strong
47	Blaud's pill	Merest trace	0.01 %	
48	Blaud's cum cascara (proprietary)	Merest trace	0.01 %	
49	Blaud's cum aloin (proprietary)	Merest trace	0.01 %	
50	Blaud's cum arsenic et strychnine	Merest trace	0.01 %	
51	" " "	Merest trace	0.01 %	
52	Blaud 'compound' strychnine	Merest trace	0.01 %	
53	Ferri alum	Merest trace	—	
54	Ferric oxide (praecip. pure)	Merest trace	0.01 %	
55	" " (sacch.)	Merest trace	Merest trace	
56	" " (calc.)	Merest trace	+ 0.02 %	
57	Ferri acetas	—	0.005 %	
58	Ferri lactas	—	0.01 %	
59	Ferri succinas	0.005 %	+ 0.02 %	Trace of lead
60	Ferri et ammonii chloridum	0.025 %	0.01 %	
61	Ferri et ammonii tartras	—	Trace	
62	Ferri citras viridis	Merest trace	0.015 %	
63	Ferri et strychninae citras	—	Trace	Trace of lead
64	Ferri albuminas	—	0.005 %	
65	Ferri et bismuthi citras	Merest trace	0.0075 %	

Copper occurs in amounts of 0.005 per cent. or more in 11 of the 65 specimens (17 per cent.), as a trace in 10 (15 per cent.), as a 'merest trace' (the lines due to copper being only just visible) in 32 (50 per cent.), and was absent from 12 (18 per cent.). Of preparations in common use in the treatment of anaemia—(a) three of the four specimens of ferri et ammon. citras contained only slight traces, while the fourth was without it, (b) Blaud's pill and its allied preparations only showed slight traces, (c) ferri carb. sacc. contained a large amount (0.0125 per cent.) in one specimen, and none in the other, (d) ferrum redactum contained amounts varying from a faint trace to 0.005 per cent.

The distribution of copper as an impurity in the preparations of iron appears to be entirely haphazard, not only as between the various preparations, but also as between different samples of each preparation. In

a clinical investigation of the use of iron in which it may be desirable to exclude any possible effects due to copper, it will not be sufficient either to select a particular preparation which may be found to be without copper or to analyse the copper content, and assume that this can then be treated as a constant. The particular sample of the preparation chosen must be adhered to throughout. The importance of this is shown by the fact that different samples from the same firm may have distinct differences in their content of copper. The table also shows that it is unsafe to attribute the value of iron preparations to their copper impurity—as has been done—since roughly one-fifth of the specimens are without copper.

Elvehjem and Lindow analysed ten salts of iron for their copper content. Their results are shown in Table II which is taken from their paper (7).

TABLE II

	Sample.	Mg. cu. per 1 grm. sample.
1	Saccharated ferrous carbonate (1)	0.0440
2	Ferrous carbonate	None
3	Ferric citrate	0.0430
4	Ferric ammonium citrate (1)	0.0204
5	Ferric potassium tartrate	None
6	Ferrous iodide syrup	0.0083
7	Saccharated ferrous carbonate (2)	0.0192
8	" " " (3)	0.0145
9	Ferric ammonium citrate (2)	0.0171
10	Saccharated ferrous carbonate (4)	0.0182

Though there are only ten examples, these results are included here because of their close general agreement with our figures, and because they are the result of chemical analysis, while ours are the result of spectrographic analysis. In two of the ten (20 per cent.) copper was absent, as against 18 per cent. in our samples. It was present in amounts that we should have described as 'traces' in 6 (60 per cent.) as against 65 per cent. in our series (i.e. in amounts of less than 0.005 per cent.). Specimens 1 and 3 would probably have been matched with lines of strength representing 0.005 per cent., which gives 20 per cent. for this group as against 17 per cent. with us.

These results confirm our conclusions regarding the irregularity of the distribution of copper as an impurity in iron salts. An instance of this can be seen in the figures for ferrous carbonate, in which our specimen (a) (0.0125 per cent.) contained very nearly ten times as much copper as their specimen 3 (0.00145 per cent.). The amount of copper is never large, but it must be remembered that it is active in the formation of haemoglobin in extremely small quantities. A patient receiving 60 gr. a day of ferri et ammon. cit. (Sample 4 of Elvehjem and Lindow) would receive in the course of three months 0.0072 grm. of copper, or $\frac{1}{8}$ gr.

Manganese is a very much more constant impurity, and occurs in much larger amounts, as might be expected from its close metallurgical association with iron. A specimen of 'pure' iron wire, though entirely free from copper, contained much more than 0.02 per cent. of manganese. In the

65 specimens, it was absent from only 1 (1.5 per cent.), occurred in traces of less than 0.002 per cent. in 16 (24.6 per cent.), and in amounts of more than 0.002 per cent. in 48 (73.9 per cent.). Of this latter group, the lines due to manganese exceeded 0.02 per cent. (the strongest amount of standard solution prepared with which they could be matched) in 13 cases. As with copper, there is considerable variation in its distribution between different samples of the same preparation, though in this case the variation is one of degree rather than of presence or absence. Thus in the case of ferri et ammon. cit. four samples show (1) a trace, (2) 0.005 per cent., (3) 0.01 per cent., (4) 0.02 per cent. If Titus, Cave, and Hughes are correct in imputing to manganese as well as copper ability to assist in the formation of haemoglobin, it is evident that the extent to which manganese is often present as an impurity must play a part in the therapeutic activities of iron. Thus in giving ferri et ammon. cit. in doses of 60 gr. a day over a period of three months the total ingestion of manganese if preparations (a), (b), and (c) in the table had been used, would be (a) 0.27 gr., (b) 0.54 gr., (c) 1.08 gr.

Other metals. The lines caused by the alkali metals and the alkaline earths have been disregarded in the description of the findings, though sodium, potassium, and calcium are almost invariably present. Traces of lead were found in five specimens, and in one of these (ferri perchlor.) the surprisingly large amount of 0.125 per cent. was present. This finding, though a solitary one, indicates that if it is intended to keep a patient for any length of time on the same sample of any particular preparation, it should be previously examined for lead, as the amount present in this sample would cause toxic symptoms.

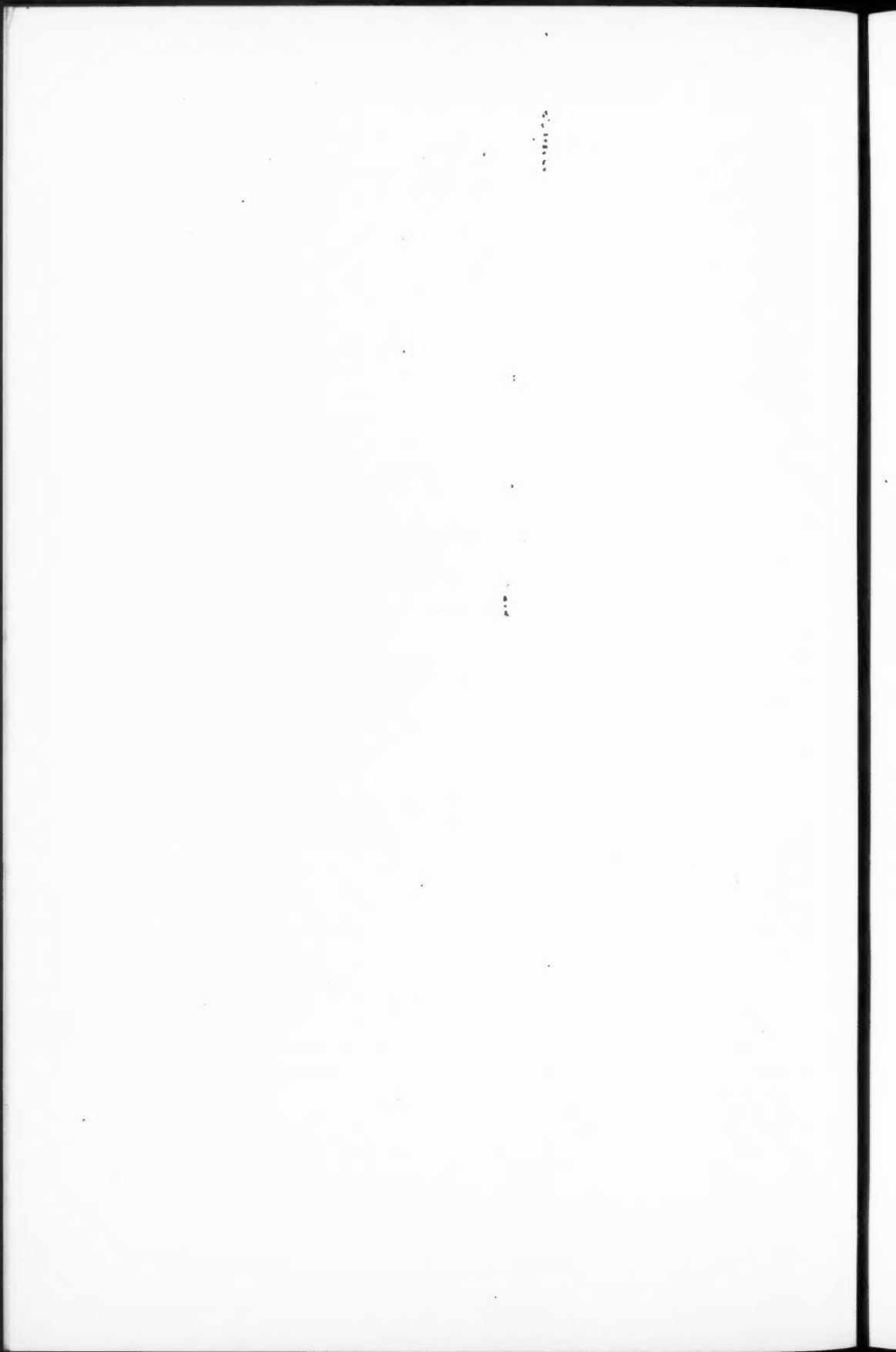
Summary

1. A spectrographic investigation of sixty-five therapeutic preparations of iron showed manganese to be a constant impurity, often present in considerable amount. Copper was absent from one-fifth of the specimens, and its distribution in the remainder was very irregular.

2. The extent to which the value of iron when given in large doses is dependent on the presence of these metallic impurities needs further investigation.

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A NEW CONCEPTION OF THE AETIOLOGY OF ERYTHEMA NODOSUM¹

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With Plates 7 and 8

FOR fifty years this condition, known by such different names as nodal fever, peliosis rheumatica, and erythema multiforme, has puzzled the medical profession. In this paper a new line of approach to the subject is described which may help to explain some of the differences of opinion held in the past.

The nodular eruption associated with the disease is its most characteristic sign, but it must not, for this reason, be considered a skin disease. Erythema nodosum has all the signs of a general body-reaction; it is preceded by an indefinite period of malaise which is followed by a more definite prodromal interval of from five to ten days during which the patient complains of headache, lassitude, anorexia, and in some cases muscle and joint pains. Fever is usually, though not always, present during this period.

The time of the occurrence of the eruption is very variable. The nodes sometimes come out with the fever, but in certain cases their appearance is delayed for as long as two to three weeks. The lesions are characteristic, appearing usually on the shins as red, raised, indurated nodules of varying size and type. They also sometimes occur on the arms, and occasionally on the face and trunk. There is little or no relation between the extent of the eruption and the severity of the general symptoms. After the appearance of the nodes most cases rapidly improve. The lesions soon fade, leaving a bruised discoloration, and the patient may recover within a week.

Although the diagnosis is only possible when the eruption occurs, we must suspect that some attacks of erythema nodosum take place when this is either absent or so slight as to pass unnoticed.

Pathology

The pathology of the lesions has been described by Wallgren and Symes. The latter concludes as follows: '(1) The lesion is an acute widespread arteriolitis in the subcutaneous fat, lasting a few hours to a few days and

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resolving rapidly without suppuration. (2) The evidence in these cases points to a soluble toxin as cause. (3) Giant cells in large numbers may accumulate in the late stages of a severe lesion: they are fat-phagocytes. There is nothing to suggest that the local presence of the tubercle bacillus accounts for them.' Although tubercle bacilli and other organisms have been described in the nodes of one or more exceptional cases (Landouzy (1)), these reports have not been confirmed. It seems probable, therefore, that the eruption represents a form of tissue 'hyper-reactivity'.

Thirty years ago erythema nodosum was considered to be in some way related to acute rheumatism. This view was due largely to the work of Mackenzie (2), who laid most stress on the type of case which is accompanied by joint and muscle pains, and often preceded by an acute sore throat. He was, however, only able to claim 15 per cent. of his total as definitely associated with acute rheumatism. For some years his views went unchallenged, but later others pointed out that only a small percentage could be shown to have any connexion with rheumatism. Fornara (3), in his review of the literature, quotes Bucher and Guisnez: the former's figures showed such an association in 8 out of 45, the latter's in 13 out of 300. Gosse (4) in a series of 100 cases did not find definite evidence of endocarditis or chorea in one. Hence, because most cases of erythema nodosum do not show these rheumatic manifestations, it has been assumed by most recent writers—Wallgren (5), Symes (6), Fornara (3), &c.—that there is no connexion between the two diseases. This may, however, be false reasoning as we shall see later.

The hypothesis that erythema nodosum is an acute specific disease caused by an unknown virus was put forward by Trousseau (7), and later supported by Lendon (8) in 1905. Lately it has found its most ardent supporter in Symes (9), who, in a paper in 1921, sums up the facts in favour of this view with admirable clarity. He states that all acute specific infectious diseases should accord with the following postulates: (1) that they are communicable from person to person; (2) should occur in epidemic outbreaks; (3) have a seasonal incidence; (4) a constant age incidence; (5) a definite and orderly sequence of events during the illness, such as an incubation period, prodromal state, febrile reaction, rash, and convalescence; (6) that immunity should be conferred by such attacks. He states that, generally speaking, erythema nodosum conforms to these postulates, and therefore should be regarded as a specific infectious disease-entity. On first sight there may be something to be said for this point of view, but it does not bear a too close scrutiny. Each single point, when considered in relation to erythema nodosum, fails to uphold his opinion when carefully examined in the light of our present knowledge of disease processes. Briefly, it may be said that, although there may be some communicability from person to person, this is indeed very slight; that epidemic outbreaks, as we shall see later, may bear a very different interpretation; that sex and age incidences also occur in other types of disease; that cases occur at all times of the

year, although possibly more at one time than another; that the incubation period, if one exists, is variable, and that an orderly sequence of events is proof only of a specific type of body-reaction, not of a specific type of virus. Finally, that the existence of confirmed immunity may well be denied—one of the children described below has already had five attacks.

Lately the hypothesis that erythema nodosum is intimately associated with tuberculosis has been gaining ground. Ernberg (10) in 1919 showed the association between early tuberculous lung conditions and erythema nodosum. He and others (Wallgren (11), Pollak (12), &c.) have shown that a high percentage of erythema nodosum patients are very hypersensitive to tuberculin, and that this hypersensitivity tends to appear at the same time as the illness of erythema nodosum. It is accompanied by the presence of phlyctenulae in 30 to 40 per cent. of cases, and gross hilar-gland enlargement can often be demonstrated by X-ray. They also state that in many instances frank tuberculous disease follows, and previous tuberculous contact may be discovered in a large number. Wallgren (13) described an epidemic germane to the present discussion which occurred in a girls' school in 1926. There were 34 girls averaging 10 years of age in the school. During a two-months' term 18 girls developed a fever, and of these 12 showed typical symptoms of erythema nodosum. At first sight this epidemic appeared clear evidence that the disease was of the nature of a specific exanthem. Further investigation, however, revealed a very close association of this outbreak and tuberculosis. All the patients were found to be positive to the Von Pirquet test, 13 showed definite pathological hilar shadows when X-rayed and 4 indefinite shadows. Of the 11 cases (1 was absent) of erythema nodosum 6 showed definite hilar enlargement. And, most significant of all, a case of active phthisis was discovered in the school. This and other evidence has led Symes and others to modify their opinion. Symes in 1928 says, '... the association of the two diseases has been so striking and dramatic, especially where erythema nodosum preceded tuberculosis, as to leave no doubt in my own mind that the two were intimately connected'. Wallgren (14), writing this year, carries his investigations further. In a series of 40 children with erythema nodosum he found 37 tuberculin positive; 13 with great, 8 with moderate, and 16 with insignificant, hilar enlargement. By a method first described by Meunier (15) he demonstrated tubercle bacilli in the sputum of 17 of these cases. Meunier's method consists in making the child cough first thing in the morning, and then washing out the stomach with 200 c.c. normal saline. The centrifugized deposit is injected into guinea-pigs, and the latter watched for the development of tuberculosis.

These investigations place beyond reasonable doubt the fact that certain cases of erythema nodosum and tuberculosis are intimately connected. It is impossible, however, to fit every case of erythema nodosum into this group, just as it is impossible to place the majority in the rheumatic group.

There is considerable divergence amongst the published figures concerning

the number of cases of erythema nodosum giving positive tuberculin reactions, but not even the most enthusiastic supporters of the tuberculous view claim more than 95 per cent. tuberculin positives. Wallgren himself admits that certain cases of erythema nodosum are tuberculin negative at the time of the attack, remain so for years subsequently, and show no connexion with tuberculosis in any way. Nor can the assertion supported by Koch (16), that such negative tuberculin reactions are due to a temporary state of anergy be maintained, for many such cases can be shown to be in good health at the time of the test. During the last $2\frac{1}{2}$ years at the Hospital for Sick Children, Great Ormond Street, only 70 per cent. (approx.) of the children with erythema nodosum have been Mantoux positive. Some of these children have been studied both during and between attacks, and have always given negative Mantoux reactions. When tested they were comparatively well and not suffering from an acute illness as is usual in cases of 'anergy'. It, therefore, must be admitted that there is a type of erythema nodosum not associated with tuberculosis. Indeed, erythema nodosum of an entirely different sort is described. Boganovitch (17) in 1930 reported five cases of erythema nodosum occurring about ten days after so-called attacks of influenza, all giving negative tuberculin reactions. Erythema nodosum is well known to occur after scarlet fever and acute tonsillitis, which usually precede the eruption by five to ten days. Lendon (18) described a nurse who had two attacks of erythema nodosum separated by a year. Each bout was preceded by an attack of acute follicular tonsillitis, the heart was involved, and she was left with a systolic murmur. Mackenzie (2) reported several similar cases in his original work in 1886. It may be concluded, then, from the literature that erythema nodosum is usually either associated with a tubercular state or is preceded by some acute infection.

The present investigation does not attempt, by giving a large number of instances, to show statistically whether most cases of erythema nodosum should be placed in either of the above groups but rather by detailed reports on a few patients to throw some new light on the pathogenesis of this most baffling condition.

Case Reports

Cases 1 and 2. Sisters, aged $3\frac{1}{2}$ and $5\frac{1}{2}$ respectively.

Past history. Neither child had had any previous illness suggestive of rheumatism or tuberculosis. The younger girl (Case 1) had had whooping-cough and broncho-pneumonia eighteen months previous to the attack of erythema nodosum about to be reported. Both children had been remarked upon as failing to thrive for some fifteen to eighteen months.

Present attacks and family history. Case 1, admitted to the ward under the care of Dr. Hutchison on March 21, 1931. Six days previously had had a vomiting attack and had been feverish. Three days before admission, spots appeared on both shins, and on the day of admission there was generalized soreness but no definite pain in any joint.

On examination the temperature was 100.2° F., and the classical nodes of erythema nodosum were present on both lower legs. No other abnormal physical signs were found.

It was noted in the *family history* that the mother had once been in a sanatorium with pulmonary tuberculosis. This note was made in a routine manner, and at the time no further significance was attached to the fact, as the child appeared to have a typical attack of erythema nodosum: the temperature settled rapidly, and recovery was complete in just over a fortnight. The child was sent home on April 1, no further investigations having been made.

On April 25, however, her elder sister, aged $5\frac{1}{2}$, was brought to the hospital with a temperature of 102° F. She was admitted to Dr. Hutchison's ward. For five months she had had frequent colds and occasional vomiting attacks. For one week she had been ill and feverish, and the mother noted sore 'spots' on the legs, but very little redness. On examination four or five definitely tender areas were found. They were slightly reddened, indurated, hardly at all raised, situated on the lower parts of the shins and on the dorsum of the feet. They were suggestive of the lesions of erythema nodosum, but by no means typical. These spots, together with the accompanying tenderness, very rapidly disappeared, leaving scarcely any bruising. The temperature and pulse-rate settled in a manner similar to Case 1.

The mother was further questioned as to her own health, and it was found that she had active pulmonary tuberculosis. Her first symptoms had occurred one year and ten months after the birth of the first child (Case 2), and seven months after the birth of the younger girl (Case 1) she was admitted to the Brompton Hospital. For the past half year she had had 'bronchial catarrh'.

The younger child (Case 1) was readmitted for investigation at the time that her sister (Case 2) was an in-patient.

Investigations.

1. Mantoux. Intradermal injection of 0.1 c.c. tuberculin (1/1000) gave a very strongly positive response in both children. This is of special significance in Case 1, as the girl was only three years of age.

2. X-ray of chest. Both patients showed definite signs of pulmonary tuberculosis.

3. Examination of sputum. The centrifugalized sediment from the stomach wash-outs was injected into three guinea-pigs.

After three weeks the guinea-pig into which sputum from the younger child had been injected showed signs of tuberculosis, and tubercle bacilli were found in the infected glands. After six weeks both the guinea-pigs injected with sputum from Case 2 also developed tuberculosis.

4. Throat cultures showed no haemolytic streptococci or other abnormal organisms.

5. Intradermal tests with haemolytic streptococcal endotoxin² were negative.

At first sight the above two cases might have been used as an argument in favour of the theory of an acute specific infectious disease spreading from patient to patient. In this they remind us of the famous epidemic in the girls' school, described by Wallgren and quoted above. When, however, the full significance of their tubercular association was demonstrated a very

² The haemolytic streptococcal endotoxin used in these cases was prepared by grinding the dead bodies of heat-killed haemolytic streptococci and extracting the residue with saline. The technique has been fully described elsewhere (19).

different interpretation was suggested. They show clearly how easy it may be to miss this tuberculous connexion in erythema nodosum unless a very careful history is taken, combined with laboratory tests and investigations.

Case 3. Girl, aged $5\frac{1}{2}$ years.

Past history. Measles and chicken-pox; no tuberculosis or rheumatism; no growing pains (or sore throats). Tonsils and adenoids removed, April 1931.

Family history. The mother had had symptoms of, and was diagnosed as suffering from, pulmonary tuberculosis in 1927—eighteen months after the birth of the child. She attended the Royal Northern Hospital, and was pronounced clear eight months ago, but was still coughing.

Present attack. She had been attending a hospital clinic with a non-infectious vaginal discharge, and was admitted to Dr. Hutchison's ward with a temperature of 100° F. on June 20, 1931.

For two weeks she had been getting thinner, was listless and off her food. One day before admission she was feverish and spots appeared on the legs. They were typical erythema nodosum, rather small and numerous. No other abnormal signs were detected. The temperature settled rapidly. Recovery was complete in ten days; she was, however, sent for prolonged convalescence.

Investigations.

1. Mantoux. In the record of the clinic from which the child was admitted it appears that a negative result was obtained to the intradermal injection of tuberculin on June 10, 1930.

On the present occasion, however, a strongly positive reaction followed the inoculation of 0.1 c.c. of tuberculin (1/1000). The skin tests were done along the extensor surfaces of the right leg on which there were no nodes at the time. The injection of tuberculin produced a lesion not unlike that of true erythema nodosum. A sketch of the legs by Mr. Charles Keogh is given on Plates 7 and 8.

2. The X-ray of chest revealed a marked increase in the hilar shadows.

3. The sediment obtained by centrifugalizing the fluid used to wash out the stomach after a period of coughing was injected into two guinea-pigs. Post-mortem examination of these six weeks after injection showed no signs of tuberculosis.

4. Intradermal injection of haemolytic streptococcal endotoxin at 1/100 dilution gave no reaction. Dick toxin (exotoxin) at 1/1000 gave a faint reaction.

5. Throat culture showed the usual throat flora of the healthy child.

6. A blood culture was performed and cultured for tubercle bacilli by Professor Okell, using Lowenstein's (20) method, and for streptococci by ourselves, using Cecil's (21) technique. Both cultures remained sterile.

Case 4. Girl, aged $1\frac{9}{12}$ years. Admitted 10.7.31.

Family history. The mother had phthisis and had come home from a sanatorium towards the end of April 1931. She was still coughing and probably had active tuberculosis. The family live in two rooms.

Past history. Sore throat six months ago. Bronchitis two months ago, for a few days.

Present illness. One week ago she became irritable, developed anorexia and constipation. She was feverish at night and complained of pain in right shoulder. She was admitted to hospital on July 10. Temperature 99° F.,

pulse 136. Indurated nodes were seen on the extensor surfaces of the legs about 2 c.c. in diameter. They were few in number and typical of erythema nodosum.

After the Mantoux test she got a sharp general reaction, the temperature reaching 105° F. and not settling to normal for four days. She later made an uneventful recovery, and was sent away for prolonged open-air treatment.

Investigations.

1. The Mantoux test was strongly positive when 0.0001 c.c. was injected intradermally. There was a general (see above) and local reaction. The latter produced a node with much induration resembling that of erythema nodosum.

2. Skin test with the haemolytic streptococcal exotoxin (Dick) gave a strongly positive reaction.

3. Skin test with the haemolytic streptococcal endotoxin was quite negative.

4. Examination of throat revealed an injected pharynx, but no haemolytic streptococci were obtained on culture.

5. The X-ray gave a picture suggestive of early tuberculosis without being definite.

6. The sputum from the stomach wash-out was injected into guinea-pigs. Post-mortem examination at the end of six weeks did not reveal the presence of tuberculosis.

Case 5.

Family history. Mother had erythema nodosum when 15 years of age. Aunt who lives with family has phthisis.

Past history. Not 'well' during last nine months. Had occasional feverish attacks during these months.

Present attack. No prodromal period reported. Attack started with sudden rise of temperature (104° F.), accompanied by the appearance of small nodes on the extensor surfaces of the legs. The eruption was diagnosed as erythema nodosum and faded rapidly, leaving a bruised appearance.

Investigations.

1. X-ray of chest showed increased hilar shadows and area of consolidation in right lung.

2. Throat culture showed normal flora of the pharynx.

3. A guinea-pig injected with the sputum obtained from the stomach wash-out developed tuberculosis in six weeks.

4. The Mantoux reaction was strongly positive.

5. The Dick test was positive.

6. The haemolytic streptococcal endotoxin reaction was faintly positive.

The above five cases have not been selected, but with the three others published here have occurred during the last six months. They are markedly similar; in each case the mother or aunt living with the family had pulmonary tuberculosis, the tuberculin reaction was strongly positive, the X-ray of the lungs showed suggestive changes in every case, and gross hilar shadows in three, while tubercle bacilli were actually demonstrated in three cases. So similar and clear cut a picture do these five children show, that even when taken by themselves they almost discountenance the possible argument that their connexion with tuberculosis is only by chance. But when they are added to all the facts accumulated by Ernberg, Wallgren, &c.

they are very strong evidence that tuberculosis is the actual causal factor in this type of case. The latter author suggests that erythema nodosum is a phenomenon of the 'initial fever of tuberculosis' (22). If contact cases are followed and examined at short intervals, it is found that six to seven weeks after contact with an infectious tubercular patient they show first signs of the disease. At this time the tuberculin reaction usually becomes strongly positive, fever is common, and although physical examination seldom reveals pulmonary signs, X-ray of the chest often demonstrates the sudden appearance of hilar shadows. It is at this time that Wallgren states that erythema nodosum occurs, the eruption being another symptom of this period of early tubercular allergy.

Apart from their connexion with erythema nodosum these cases are of interest. They illustrate that the method of stomach lavage for demonstrating the presence of tubercle bacilli in children is both simple and efficient. It is important to note that children without any physical signs and apparently in good health can yet have tubercle bacilli in their sputum. Case 1 is a good example of this: she was discharged from the ward having apparently quite recovered from her attack of erythema nodosum, and it was only on subsequent readmission for investigation that tubercle bacilli were shown to be present by stomach wash-out and definite signs of tuberculosis observed by X-ray. They illustrate the immense importance of realizing the intimate connexion between tuberculosis and erythema nodosum, and make it plain that it is the duty of every physician to bear this in mind when dealing with cases of the disease.

Case 6. Girl, aged 9 years.

Family history. No tuberculosis or rheumatism in the family.

Past history. In 1927 she was admitted to an isolation hospital for scarlet fever suffering from acute sore throat. Ten days later spots appeared on the legs, which from the account suggest the lesions of erythema nodosum. She got well but joint and limb pains persisted, and she attended the Hospital for Sick Children, Great Ormond Street, for subacute rheumatism. In February 1928 she had a typical attack of erythema nodosum following an acute sore throat and accompanied by acute polyarthrititis. In July 1929 and June 1930 she had two more similar attacks, always preceded by a severe sore throat. On each occasion she was an in-patient at this hospital.

Present attack. On June 5, 1931, the child attended the hospital, complaining of sore throat and some joint pains. The mother predicted that 'the spots would come out soon'. This proved to be the case, and six days later the eruption appeared and the child was admitted to the ward under Dr. Hutchison.

The nodes on the legs were large, indurated, and painful. She had little fever and less joint pains than in the previous attacks. The illness ran its usual course and she was convalescent in a week.

Investigations.

1. A throat culture was taken during the previous sore throat, and again seven days later after the eruption had appeared. The first culture showed

an almost pure growth of haemolytic streptococci on blood-agar, while the second gave no haemolytic colonies.

2. Intradermal tests with haemolytic streptococcal endotoxin in the arm at the time of the sore throat gave a strong positive reaction, and when repeated while the patient was in hospital on the skin of the right leg, produced a lesion resembling the true node of erythema nodosum in every way. It appeared in twenty-four hours, increased to 40-50 mm. in forty-eight hours, taking the form of a large, red, indurated node which faded slowly in seven days, leaving a bruised appearance. A sketch of the two legs showing the real and artificial nodes is given on Plates 7 and 8. The skin test with haemolytic streptococcal exotoxin (Dick toxin) was negative.

3. The Mantoux test was performed during a normal period in 1930, also during the preceding sore throat, at the height of the attack, and during convalescence, and was always negative.

4. X-ray of the chest showed no hilar enlargement.

5. The deposit from the stomach wash-out was injected into a guinea-pig. The pig was killed and examined after six weeks. No tuberculous infection was found.

To sum up. This patient had five attacks of erythema nodosum, each preceded by a sore throat and accompanied by acute rheumatic manifestations. The throat culture at the time of the sore throat revealed the presence of haemolytic streptococci which rapidly disappeared from the throat. Skin tests showed a marked reaction to haemolytic streptococcal endotoxin, while no evidence of tuberculosis was found either by physical examination, Mantoux reaction, or X-ray.

Case 7. Girl, aged 9 years.

Family history. No family history of tuberculosis or rheumatism.

Past history. Whooping-cough, measles. In March 1931 the child developed a fever accompanied by joint pains. Five days after the onset nodes appeared on the extensor surfaces of the legs. The illness ran the usual course of erythema nodosum.

Present attack. The child was admitted to Dr. Hutchison's ward on June 23, 1931, with erythema nodosum. Before admission she had suffered from fever and joint pains for one week. On admission the eruption was beginning to fade. It consisted of large somewhat diffuse dark-red indurated nodes. The patient made an uninterrupted recovery.

Investigations.

1. Although the child did not complain of sore throat, examination revealed an injected and inflamed pharynx, and throat culture showed the presence of haemolytic streptococci in preponderating numbers.

2. Intradermal injection of haemolytic streptococcal endotoxin produced a node resembling strongly the ordinary lesions of erythema nodosum. It faded in four days, leaving a bruised appearance.

3. The haemolytic streptococcal exotoxin (Dick) gave a weak, rapidly fading reaction.

4. The Mantoux reaction was negative.

5. X-ray of the chest showed slightly increased hilar shadows, but nothing definite.

6. The sputum (gastric lavage) was injected into two guinea-pigs. Post-mortem examination of these in six weeks did not reveal the presence of tuberculosis.

Case 8. Girl, aged 8 years.

Family history. No family history of tuberculosis. An aunt had rheumatic fever when a child. Two sisters were alive and well.

Past history. Measles, whooping-cough, and chicken-pox. No history of scarlet fever, tonsillitis, or colds.

Present illness. Admitted to the Hospital for Sick Children, Great Ormond Street, under Dr. Poynton, on February 26, 1931. Previous to admission she had complained of pains in the legs for one month. One week before admission developed an upper respiratory infection.

On admission her temperature was 101° F., and there was swelling of the knees and wrists, accompanied by much pain. From the knees to the toes the typical eruption of erythema nodosum was present. The lesions were large, measuring 20–50 mm., and were painful. The joint pains flitted from joint to joint, the heart was dilated and the first sound roughened. She responded readily to treatment with aspirin. Dr. Poynton considered the case as allied to acute rheumatic fever.

Investigations.

1. The X-ray of the chest showed no abnormal manifestations.
2. Intradermal skin tests with 0.0001 c.c. tuberculin and 0.001 c.c. 'haemolytic streptococcal endotoxin' on February 29, 1931, gave a completely negative reaction to the former, while the latter produced on the arm an indurated red node not unlike the true lesion of erythema nodosum. These tests were repeated on June 28, 1931, and again gave a negative tuberculin and a strongly positive endotoxin reaction.
3. A blood culture was taken, using the same method as for Case 6. Both tubes were sterile at the end of six weeks.
4. No sputum was obtained for injection into guinea-pigs in this case.

The last three cases again fall into a very definite group, but the whole picture is different from the type already described as formed by Cases 1–5. Cases 6, 7, and 8 appear to have no connexion with tuberculosis but to follow nasopharyngeal infections. In two of the above cases haemolytic streptococci were cultured from the throat, and in all three the intradermal injection of haemolytic streptococcal endotoxin produced nodes resembling those of erythema nodosum.

If Table I is examined it will be seen how clearly the first five cases fall into one group and the last three into another. Not only do the laboratory investigations, such as skin tests, X-rays and sputum examinations, give completely different results in the two types, but the clinical picture also tends to be somewhat distinct. This is most marked in severe cases of either group. The period of malaise in the tubercular cases is characterized by listlessness and loss of weight, in the streptococcal cases by subacute rheumatism. The prodromal period in the former is often associated with high fever and general aching pains, but in our cases at least, by no arthritis. In the streptococcal cases this period is associated with an acute nasopharyngeal infection and often the development of severe polyarthritis of a rheumatic type. In both, soon after the appearance of the eruption, the symptoms tend to subside. Although the above cases are too few in number to justify dogmatism, it has seemed to us that the eruption itself is

TABLE I

Skin Tests.

Case No.	Sex.	Age.	Yrs.	Mantoux.	Haem. Strept. Endotoxin.	X-ray of Chest.	Guinea-pig Inoculation.	Family History of Tuberculosis.	Past History of Rheumatism or Tuberculosis.	No. of Attack of Erythema Nodosum.	Type of Lesion.	Throat Infection Preceding Attack.	Joint Pains.	Tuber- culous Type.
1	F.	3½	+	+	0	Gross hilar shadows	Tuber- culosis in 3 wks.	Mother phthisis	Nil	1st	Few small	Nil	Nil	Tuber- culous
2	F.	5½	+	+	0	Gross hilar shadows	Tuber- culosis in 6 wks.	Mother phthisis	Nil	1st	Very few small	Nil	Nil	Tuber- culous
3	F.	5½	+	+	0	Definite hilar shadows	Nil	Mother phthisis	Nil	1st	Many small	Nil	Nil	Tuber- culous
4	F.	1½	+	+	0	Suggestive enlargement	Nil	Mother phthisis	Nil	1st	Moderate	Nil	Nil	Tuber- culous
5	F.	7	+	+	+	Lung con- solidation	Tuber- culosis in 6 wks.	Aunt phthisis	Nil	1st	Small	Nil	Nil	Tuber- culous
6	F.	9	0	+	+	Normal	Nil	Nil	Subacute rheumatism 3 yrs.	5th	Few large indurated	Present	Severe	Strepto- cocal
7	F.	9	0	+	+	Insigni- ficant hilar shadows	Nil	Nil	Nil	2nd	Large diffuse	Present	Present	Strepto- cocal
8	F.	8	0	+	+	Normal	—	Nil	Rheumatic pains for 1 month pre- viously	1st	Large in- durated	Present	Severe	Strepto- cocal

+++ = very strong positive reaction.

0 = no reaction.

+ = weak positive reaction.

TABLE II

Case No.	Sex.	Age.	Skin Tests.			X-ray of Chest.	Guinea-pig Inoculation.	Family History of Tuberculosis.	Past History of Rheumatism or Tuberculosis.	No. of Attack of Erythema Nodosum.	Type of Lesion.	Throat Infection Preceding Attack.	Joint Pains.	Type.
			Haem. Strept. Endotoxin.	Mantoux.	Yrs.									
1	M.	11	(+)	++		(Gross hilar shadows)	—	Father ? phthisis	Nil	1st	—	? Sore throat	Nil	Tuber- culous
2	F.	6	(0)	++		(Suggestive hilar shadows)	—	Nil	Nil	1st	—	Nil	Nil	Tuber- culous
3	M.	4	(0)	(+++)		(Gross hilar shadows)	—	Nil	Nil	1st	—	Nil	Nil	Tuber- culous
4	F.	10	(+++)	++		(Suggestive hilar shadows)	—	Indefinite family history of T.B.	Nil	1st	Small many	Nil	Nil	? Tuber- culous
5	F.	4	(++)	(++)		(Insignificant hilar shadows)	—	Nil	Nil	1st	—	Present	Present	? Strepto- coccal
6	F.	12	—	0		—	—	Nil	Rheumatic fever 3½ yrs. ago	1st	—	—	Severe	? Strepto- coccal

+++ = very strong positive reaction.

+ = weak positive reaction.

(+) = not tested during attack but subsequently.

0 = no reaction.

somewhat different in the two types. In the tubercular cases the nodes are often present in considerable numbers, not only on the legs, but sometimes on the arms and face. They are usually not more than 20 mm. in diameter, and at first of a light-red colour. The eruption in the streptococcal cases, in our series, has been larger, up to 50 mm., more indurated and of a darker colour and took longer to fade (see Plates 7 and 8). It appears that the streptococcal cases are apt to get recurrent attacks if again exposed to acute nasopharyngeal infections, while I have not observed a second attack in a tubercular case.

Table II consists of the notes of six children who were admitted to this hospital during the last two years, but not seen at the time by the author. They are included because they demonstrate several important points. Five of the patients have been subsequently examined and these recent findings are shown in brackets in the table. In this series several patients were sensitive both to tuberculin and to haemolytic streptococcal endotoxin as might be expected in such an age group, indeed we may consider ourselves fortunate in having so clear cut a series in Table I. In spite of this difficulty and the fact that they were not studied by us during the attack, all the cases appear to fit into one or other group with a fair degree of certainty. Cases 1-3 belong almost surely to the tubercular type. Case 4 is somewhat doubtful, as both skin tests were strongly positive when seen later, but the picture of the case when taken as a whole is that of the tubercular type. In Case 5 the skin tests were also both equally positive, but here there was a definite history of sore throat preceding the attack which was accompanied by pains. It should probably be placed in the streptococcal group, as should Case 6.

Discussion

The facts presented in this investigation show that both tuberculosis and acute streptococcal infection play a part in the aetiology of erythema nodosum. Therefore, those who hold that it is intimately connected with the rheumatic state and those who point out its association with tuberculosis are right, though both are wrong when they try to include all cases in one or other group.

In the past the relationship between erythema nodosum and acute rheumatism was obscured owing to the fact that the connexion of both conditions with acute streptococcal throat infections was not clearly understood. Recently the work of Glover (23), and the observations of Schlesinger (24) and Sheldon (25), have thrown a new light on the problem of acute rheumatic fever. The latter have shown that sore throats are apt to be followed in rheumatic patients by secondary attacks of acute rheumatic fever after a silent interval of ten to twelve days. Collis (19) has pointed out this year that there is no essential difference between these secondary attacks and primary acute rheumatic fever and that both are apt to follow

acute throat infections with the haemolytic streptococcus. Coburn's (26) recent work in America agrees entirely with these observations. Both Coburn and Collis found rheumatic patients very hypersensitive to products of the haemolytic streptococcus—Coburn used what he called haemolytic streptococcal 'nucleoprotein' and Collis haemolytic streptococcal 'endotoxin' for these tests. Both probably contain the same active principle.

In this paper I have shown that a certain type of erythema nodosum is apt to follow acute haemolytic streptococcal throat infection, and that not only are these patients very hypersensitive to the haemolytic streptococcal endotoxin, but that the injection of this substance intradermally in such cases will actually produce a lesion indistinguishable from that of the typical node of erythema nodosum.

The actual number of cases falling into the tuberculous or streptococcal type undoubtedly depends on locality; here in London a fair number are streptococcal, while in Scandinavia the majority appear to be tubercular. It is of course quite possible that other acute infections may also play a similar role in isolated instances, but we have no actual experience of such cases ourselves.

The pathogenesis of the condition is not completely explained by these observations. Dr. Robert Hutchison (personal communication) suggests that while the actual eruption of erythema nodosum may be non-specific and may occur in various conditions, yet there exists the entity 'nodal fever'—an acute specific disease. The cases presented above cannot be said to support this view in that all show the general classical picture of erythema nodosum and some are typical in every feature showing prodromal period, febrile reaction, eruption, convalescence, &c., and yet each was definitely associated with either tubercular or streptococcal infection. Fornara (3) recently suggested that erythema nodosum is caused by a specific virus, but that the eruption only appears when the patient is in the allergic state and consequently, as tuberculin is the commonest allergen, that it is most frequently associated with tuberculosis. This argument, though plausible, is illogical, for the introduction of another factor in the form of an unknown virus not only fails to explain the phenomenon but confuses the issue. Why should such a virus only be able to act when the subject is hypersensitive to the germ of another disease? Surely it is best to build our hypothesis merely on the facts we possess and to suppose that erythema nodosum is a type of general tissue response to different bacterial allergens, its most characteristic feature being the nodular eruption. In the case of tuberculosis this takes place five to six weeks after the initial infection, and in streptococcal cases in five to twenty days.

The following observation made by Dr. Thursfield in 1924, but never published, strongly supports the above hypothesis.

A girl, aged 11 years, admitted to Dr. Thursfield's ward, Hospital for Sick Children, Great Ormond Street, 18.3.24, for diagnosis, being a suspected case of early tuberculosis.

Family history. The father died of phthisis and there was a history of contact with a sister who was suffering from pulmonary tuberculosis.

Condition on examination. She appeared quite well, there were no signs of tuberculosis in the lungs or elsewhere. The X-ray of the chest was normal.

On 22.3.24 the child was given 0.005 c.c. of old tuberculin subcutaneously. There was an immediate reaction, the temperature rising to 102° F. This reaction continued for almost two weeks, the temperature running a swinging course between normal and 102°. On the eighth day nodes resembling those of erythema nodosum in every way appeared on the extensor surfaces of the legs. After the appearance of the eruption the patient rapidly improved and the temperature reached normal on the thirteenth day; the nodes faded in the usual manner.

The experiment was repeated a month later on 2.5.24 and again 0.005 c.c. of old tuberculin was injected subcutaneously. An eruption immediately came out on the legs indistinguishable from erythema nodosum. On this occasion there was no rise of temperature or general reaction after the injection of the tuberculin. The eruption again faded and the child made an uninterrupted recovery.

I was able to get in touch with the girl again in July 1931. She was in good health and had had no symptoms of tuberculosis during the last seven years.

The above case is, I believe, unique and goes a long way to explain the aetiology of the disease. Had the child only received one injection of old tuberculin the argument might have been advanced that she was about to have an attack of erythema nodosum in any case, but the repetition of the phenomenon after the second injection is as near proof as can be that the injection of tuberculin actually caused the eruption in this case.

The facts presented in this paper suggest that the eruption of erythema nodosum is produced by a soluble break-down product of certain organisms acting on already hypersensitive tissues, though the actual pathology of the lesions needs further detailed study before this theory can be proved.

Summary

1. Five cases of erythema nodosum intimately associated with tuberculosis, in three of whom tubercle bacilli were found in the stomach wash-out, are described.

2. Three cases following streptococcal sore throats are given in detail. These patients gave strongly positive skin reactions to haemolytic streptococcal endotoxin, while all three were negative to tuberculin.

3. Six cases not seen during the attack are reported. Four of these fit into the tubercular and two into the streptococcal type.

4. A case of suspected tuberculosis is described, in which the injection subcutaneously of 0.005 c.c. of old tuberculin caused an eruption, indistinguishable from erythema nodosum, to appear on the legs, and was associated with a thirteen-day febrile reaction. A second similar injection a month later again produced a similar eruption, but this time without a general febrile reaction.

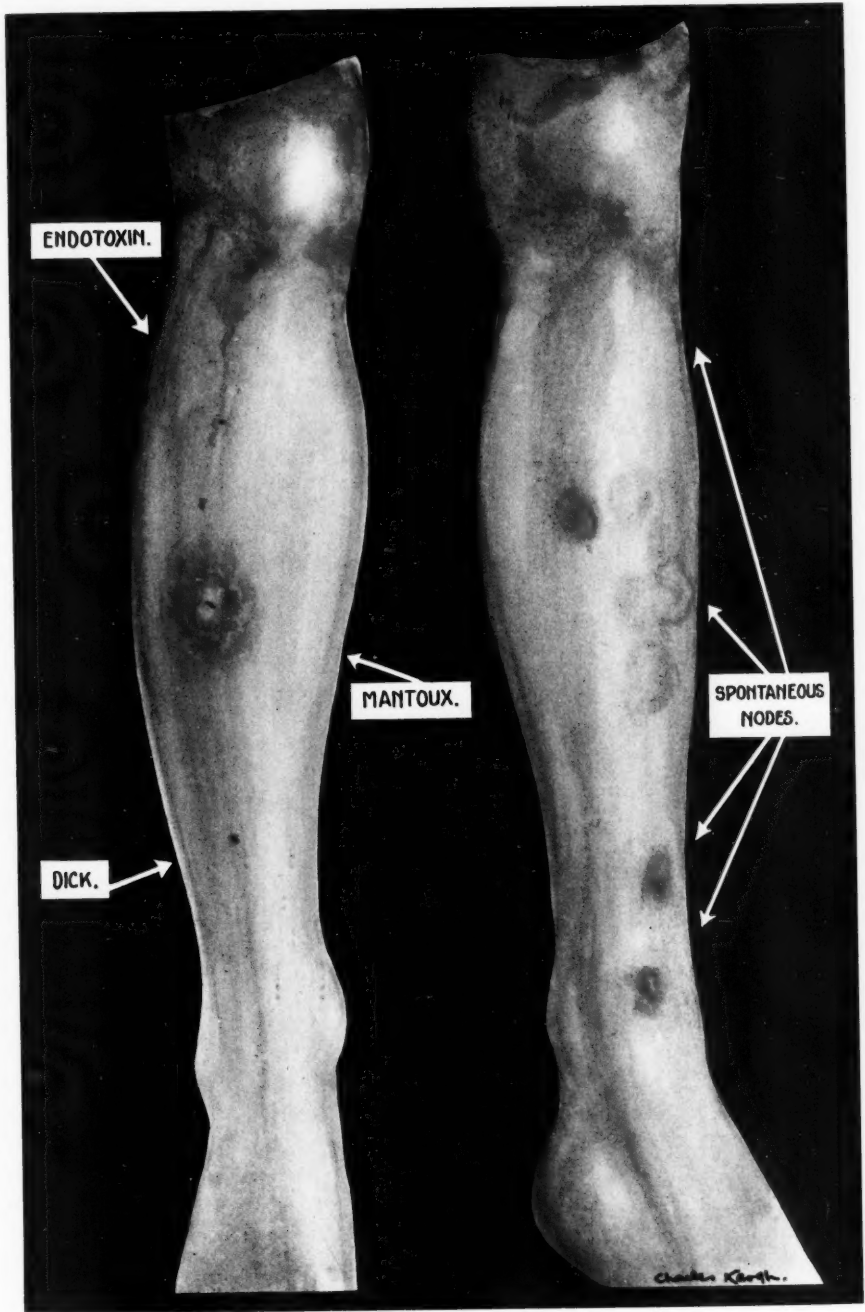
5. The above facts suggest that erythema nodosum is a type of hyper-reactive tissue response to different bacterial allergens and that the allergens responsible for erythema nodosum in London are commonly tuberculin and haemolytic streptococcal endotoxin.

I wish particularly to thank Dr. Robert Hutchison for his help and advice throughout this work, and Dr. C. E. Lewis for his co-operation and help with many of the cases. I am most grateful to Dr. Thursfield, Dr. Nabarro, Mr. Keogh, and the medical staff of the hospital.

I should also like to thank Mr. J. A. G. Swan for his most valuable technical assistance. The work has been done with assistance of the Sebag-Montefiore Research Fund and the Medical Research Council.

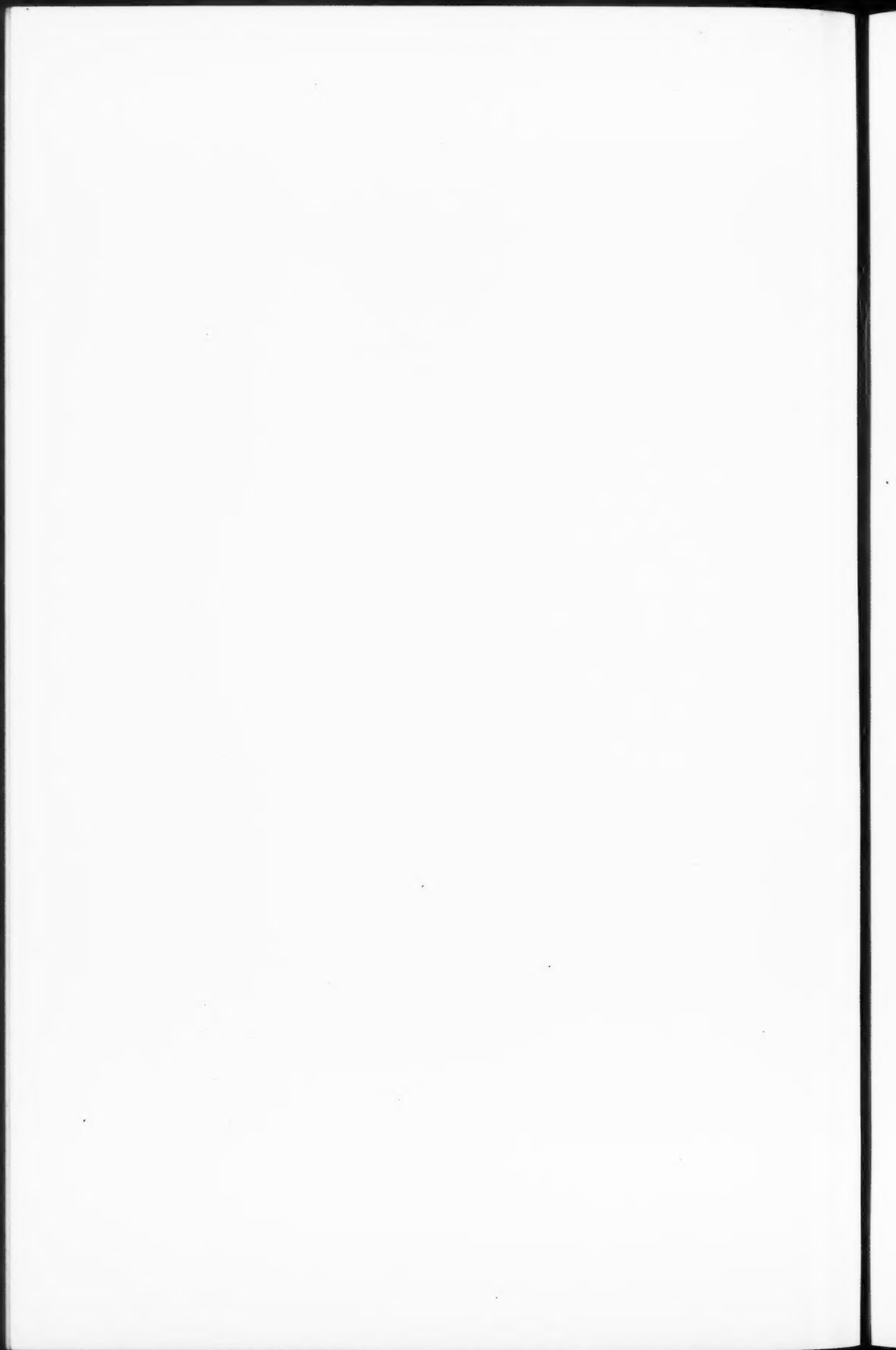
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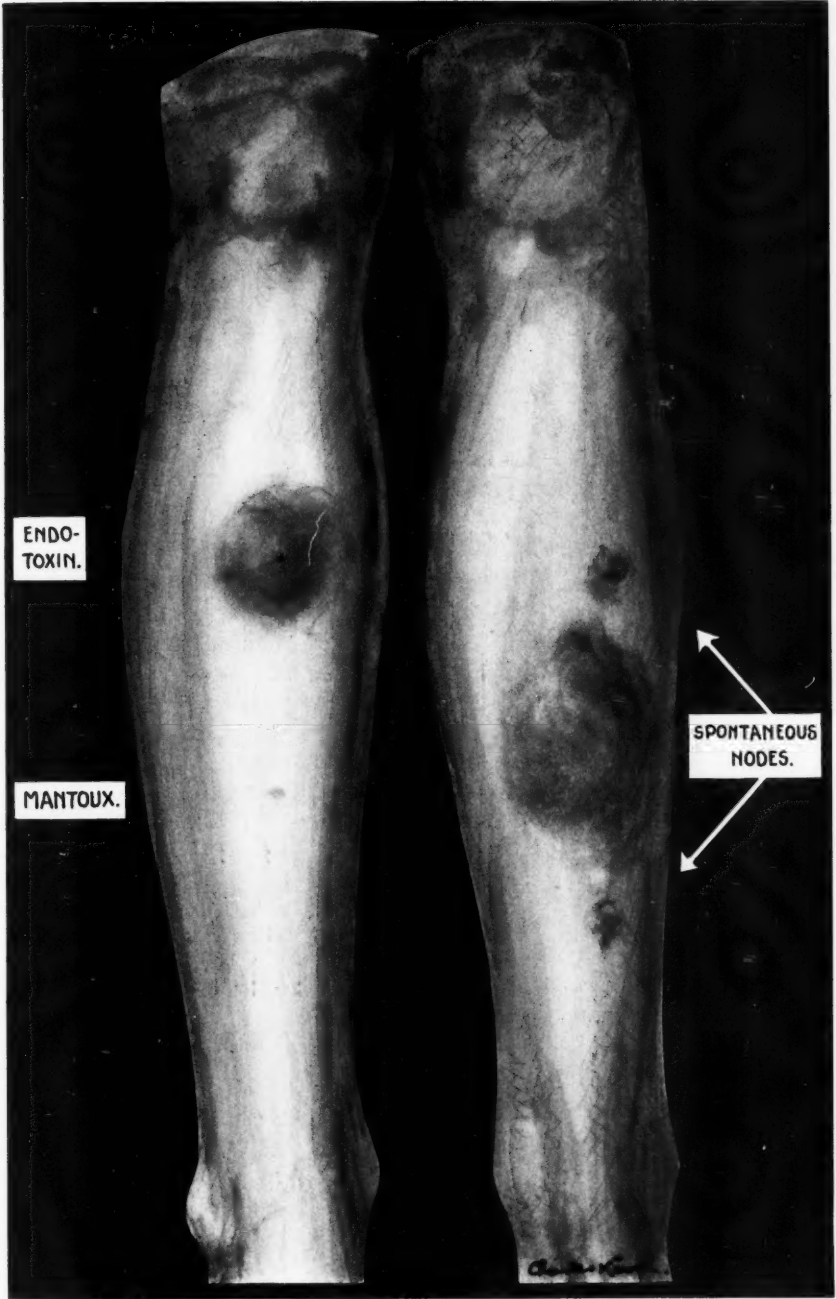
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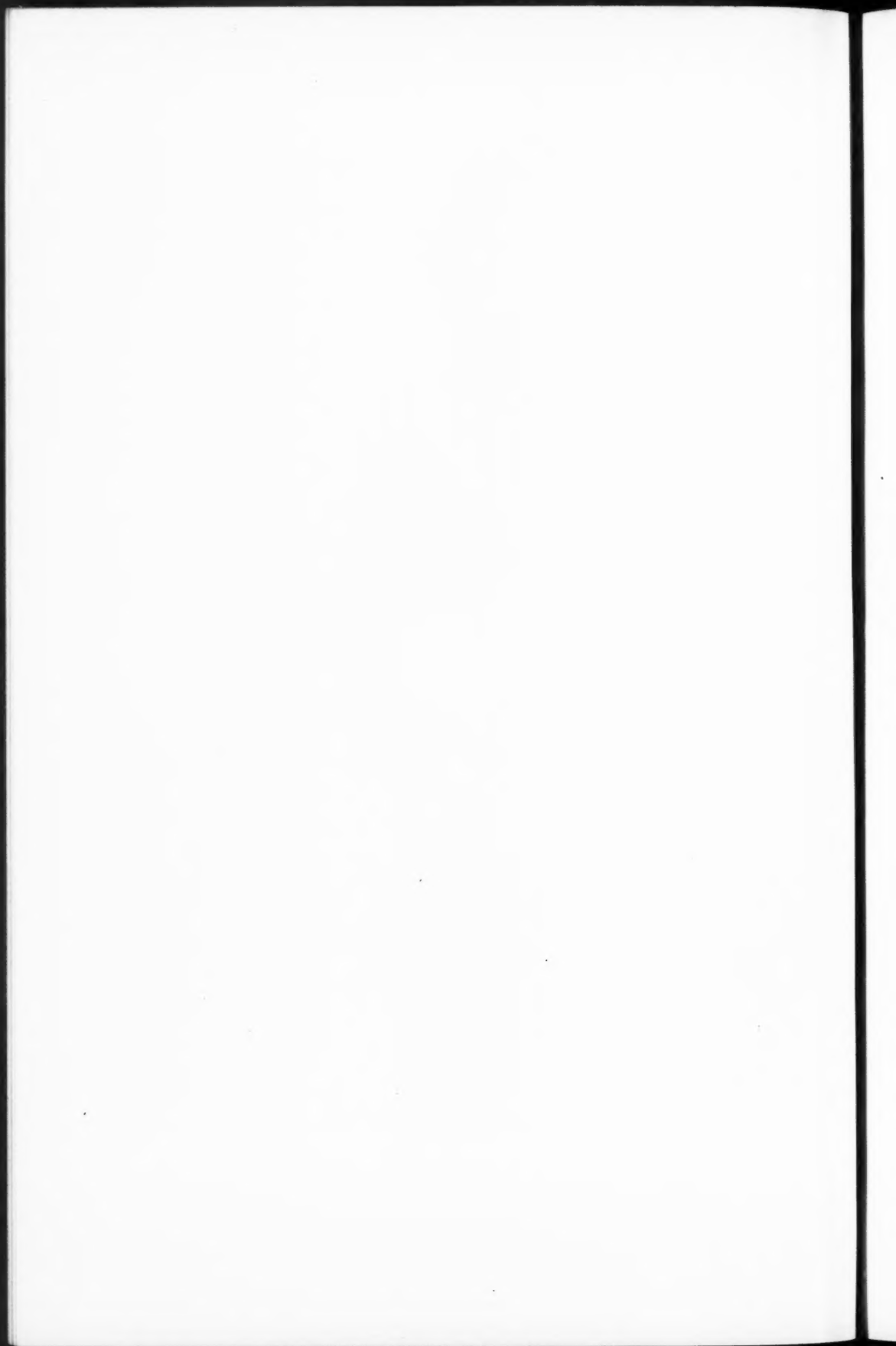
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ACHLORHYDRIA AND ACHYLIA GASTRICA, AND THEIR CONNEXION WITH THE ADDISON'S ANAEMIA-SUB- ACUTE COMBINED DEGENERATION SYNDROME AND SIMPLE (NON-ADDISONIAN) ACHLOR- HYDRIC ANAEMIA¹

By ARTHUR F. HURST

SINCE 1897, when Martius first drew attention to the absence of free hydrochloric acid from the gastric contents in Addison's anaemia, it has gradually become recognized that the association is almost, if not quite, invariable, though with the exception of a clinical lecture on achylia delivered by Robert Hutchison in January 1909, little attention was given to the subject in England until the last ten years, and no mention of achlorhydria is made in the article on pernicious anaemia in the editions of two of the most popular British text-books of medicine published shortly after the War.

In this paper I shall describe the different causes of achlorhydria and how each may give rise on the one hand to Addison's anaemia and subacute combined degeneration of the cord, and on the other to simple achlorhydic anaemia.

Age and Sex Incidence of Achlorhydria

Dr. J. S. Hartfall has recently analysed the results of fractional test meals given to 2,448 patients at New Lodge Clinic: his conclusions will be published in the *Guy's Hospital Reports* for January 1932. Excluding 20 cases of achlorhydria artificially produced by gastro-jejunostomy and 21 cases associated with carcinoma of the stomach and 51 with Addison's anaemia, two diseases which occur chiefly between the ages of 50 and 70, there remain 2,356 patients of whom 242, or 10.3 per cent., had achlorhydria. Table I shows its incidence at different ages. From 10 to 19 the incidence is 4 per cent., which is identical with that found by Bennett and Ryle in 100 normal students. There is a rise of 4 per cent. to the 30-39 period and the same rise to the 40-49 period, but in the next three decades taken together there is a rise of only another 4 per cent.

The slight increase in the incidence with advancing years is clearly the

¹ Received September 30, 1931.

result of chronic gastritis. The majority of patients never recover from achlorhydria due to this cause, and as fresh cases must arise as a result of food poisoning, acute infections, and oral and nasopharyngeal sepsis at every age, it is surprising that the incidence between 70 and 79 is only 4 per cent. greater than between 40 and 49, and that this is only 8 per cent. greater than between 10 and 19.

TABLE I. *Percentage of Achlorhydria at different ages, excluding 21 cases of carcinoma of the stomach and 51 of Addison's anaemia with achlorhydria and 20 cases of achlorhydria following gastro-jejunosomy or partial gastrectomy.*

Age.	Total Number of Test Meals.	Achlorhydria.	
		Total.	Percentage.
10-19	53	2	4
20-29	257	17	7
30-39	484	39	8
40-49	608	76	12.5
50-59	607	58	10
60-69	297	41	14
70-79	48	8	16.6
80-89	2	1	
10-89	2,356	242	10.3

TABLE II. *Relative frequency of Achlorhydria in males and females.*

	Total Number of Test Meals.	Achlorhydria.	
		Total.	Percentage.
Male	1,207	90	7.5
Female	1,149	152	13.2
Total	2,356	242	10.3

In the past it has been said that achlorhydria is so common in elderly people that its discovery in a case of suspected carcinoma of the stomach is of no help in diagnosis. The earlier observations which led to this conclusion were made with the Ewald test meal, which always gives a higher percentage of achlorhydria than a fractional test meal. In 1930 Davies and Jones investigated 100 healthy institution inmates between the ages of 60 and 95 by the fractional method. They found achlorhydria in 32—i.e. more than double the percentage found at New Lodge Clinic in 347 patients of similar age, in spite of the fact that a large majority of the latter were examined on account of digestive symptoms, so that the incidence of achlorhydria among healthy people of the same class and age would probably be considerably lower. The much higher incidence of achlorhydria among elderly people of the hospital class than among private patients of the same age must be due to the greater frequency of gastritis among the former due to poorer and less well-prepared food and less attention to oral hygiene.

The New Lodge Clinic statistics reveal the curious fact that the incidence of achlorhydria is definitely greater in women than in men (Table II).

Thus it was present in 90 out of 1,207 men (7.5 per cent.) compared with 152 out of 1,149 women (13.2 per cent.).

Causes of Achlorhydria

A. *Achylia gastrica*. The achlorhydria in achylia gastrica is due to permanent inability of the gastric mucous membrane to secrete free hydrochloric acid. This is often, but not always, associated with inability to secrete pepsin.

(i) *Constitutional achylia gastrica*. Martius in 1897 expressed the belief that the majority of cases of achlorhydria are primary or constitutional. On the other hand, the investigations of Faber, begun a few years later, led him to the belief that achlorhydria is always secondary to gastritis. I am convinced, however, that an hereditary, familial condition exists, in which no hydrochloric acid is produced by the gastric mucous membrane owing to an inborn error of secretion, though it may be less common than we believed at one time, as the investigations of Bennett and Ryle (1920) on 100 normal students, four of whom had achlorhydria, were made at a time when the possibility of other causes of achlorhydria was not as fully recognized as it is now. None, however, of the four students with achlorhydria had ever suffered from indigestion, and each was found to have complete achlorhydria when a second test meal was given. Subsequently Baird, Campbell, and Hern found achlorhydria in one out of fifty-seven students, and Apperley and Semmens in eight out of ninety students, the total for the three series giving a percentage of 5. At least two of the last series were definitely constitutional, as the father of one had died from Addison's anaemia, and the mother of another had previously been found to have achlorhydria associated with rheumatoid arthritis. In 1924 Wright found achlorhydria in 4 out of 250 healthy children between the ages of 6 and 17, but one of them when re-examined a year later was found to have free acid in the test meal, so the achlorhydria must have been due to gastritis. Probably the true incidence of constitutional achylia is not more than 2 per cent.

Achlorhydria is often observed in infancy, and though in many instances it may be a result of gastritis, in others it is undoubtedly due to constitutional achylia. This was probably the cause of the achlorhydria found by Hampson and Warner in a female infant of eight months with the typical blood-picture of Addison's anaemia; recovery followed treatment with liver extract. Seventeen families, including two under my care, have been recorded in which achylia was present in two or more members, none of whom had anaemia or nervous symptoms. Martinez has in addition observed more than twenty such families, in one of which the grandmother, her daughter, four grandchildren, and five out of thirteen great-grandchildren had achylia. Wilkinson and Brockbank have recorded a family in which the great-grandfather, both of his children, his only grandchild, and

only great-grandchild had chronic diarrhoea; the great-grandfather and one of his daughters were dead, but the other daughter and her daughter and granddaughter had achylia and were completely relieved by hydrochloric acid.

In constitutional achylia gastrica histamine produces no secretion of acid, and the investigations of Wilkinson and Brockbank on familial cases show that in at least 50 per cent. no pepsin is secreted. In uncomplicated cases no mucus is present in the gastric contents, but owing to the absence of gastric juice, which normally dilutes and softens any irritants which may be swallowed, chronic gastritis often develops; and owing to the absence of the antiseptic hydrochloric acid the inflamed mucous membrane is likely to become secondarily invaded by swallowed bacteria from the gums, throat, and nose.

The occurrence of constitutional achylia gastrica explains the frequent familial incidence of the various diseases to which achlorhydria may give rise. In seven out of a series of twenty-four private cases of Addison's anaemia and three out of fifteen of subacute combined degeneration of the cord (25 per cent.) there was a history of Addison's anaemia in one or more members of the family. In nine cases achylia gastrica was present without Addison's anaemia or subacute combined degeneration in other members of the family of patients with Addison's anaemia. In 1928 I collected most of the published cases; more recently Wilkinson and Brockbank have made a still more complete investigation of the literature and have added numerous cases of their own. Including my own cases and theirs there are 140 families in which two or more members in 1, 2, 3, or 4 generations were affected with Addison's anaemia with or without subacute combined degeneration, and 59 families in which Addison's anaemia or subacute combined degeneration of the cord was present in one or more members and achylia in others, including a few in which Addison's anaemia, subacute combined degeneration of the cord, and achylia were each present in different members. Investigations into the frequency of achylia in the relatives of patients with Addison's anaemia have shown that 70 out of 291 relatives (24 per cent.) had achylia (Wilkinson and Brockbank). The relatives may be of any age and often include children: thus Weinberg records the case of a man with Addison's anaemia who had four children; of these a boy of ten, a boy of six, and a girl of four had achylia.

Constitutional achylia gastrica may also give rise to simple anaemia. Consequently both forms of anaemia may occur in the same family. The father of a female patient of mine with severe simple achlorhydric anaemia had Addison's anaemia; and the mother of one and the sister and two maternal aunts of another patient in Witt's series died of Addison's anaemia. Gram recorded the case of a father and two sons who had Addison's anaemia, one daughter in 1921 having simple achlorhydric anaemia; nine years later she had developed Addison's anaemia, which was cured by liver, and another daughter had simple achlorhydric anaemia which was uninfluenced by liver, but cured by iron. Mustelin also records a family in

which a woman, her maternal aunt and female cousin had Addison's anaemia, and a sister had simple achlorhydric anaemia.

(ii) *Atrophic gastritis*. In a monograph on 'Atrophy of the Stomach', published in 1880, Samuel Fenwick described how this condition, which he showed could not be due to post-mortem digestion and which he regarded as degenerative rather than inflammatory in origin, was found in a small proportion of fatal cases of Addison's anaemia. He regarded the anaemia as a result of deficient digestion of proteins resulting from a loss of the normal secretion of pepsin. The true nature of this atrophy remained unexplained until 1904, when Faber discovered that post-mortem digestion of the mucous membrane could be prevented by injecting 100 c.c. of 10 per cent. formalin into the abdominal cavity immediately after death. Working with Lange (1908) he found that patients dying from Addison's anaemia associated with achlorhydria showed every grade of chronic gastritis from simple infiltration of the glands of the mucous membrane with inflammatory products with no trace of atrophy, to partial or complete atrophy of all the secreting tubules. He showed in this way that atrophic gastritis is the end result of chronic diffuse gastritis, but is by no means essential for the production of achlorhydria. He still believes that the latter is always the result of gastritis, even when all the secreting tubules are intact. But if this were true, it is difficult to see why the gastritis and the achlorhydria to which it gives rise should not be curable; in some cases they undoubtedly are, as I shall presently show, but in many cases the achylia appears to be constitutional and the gastritis is secondary. Faber also noted that complete atrophy is often found associated with the achlorhydria of old people, although their blood may have been perfectly normal.

In some cases of atrophic gastritis mucus may be present in the gastric contents, but in the final stages of atrophic gastritis the mucus-producing cells also atrophy so that no mucus can be secreted.

The presence of a deposit of squamous epithelium, to which Davies has recently drawn attention, is of no diagnostic significance: Ganz, working in my clinic in 1925, found that the number and character of the cells in each case are parallel with those of the cells found in the spittle, from which they are certainly derived.

I have seen many cases of Addison's anaemia and subacute combined degeneration of the cord without any family history, in which the onset of symptoms presumably due to achlorhydria dated from an attack of acute gastritis. It is generally impossible to say whether the latter led at once to destruction of the secreting tubules, or whether the achlorhydria was the result of a still recoverable chronic gastritis, but when a test meal shows a low total acidity and there is no mucus it is probable that atrophic gastritis is present. The following is an example of such a case.

Addison's anaemia following atrophic gastritis, the result of food poisoning. Recovery with transfusion, tonsillectomy, and hydrochloric acid. A man of 62 had an attack of acute food poisoning with abdominal pain, vomiting, and

diarrhoea in 1914. This was followed by chronic diarrhoea, which was still present in 1922, when the first symptoms of Addison's anaemia developed. Some months later, when he came under our observation with severe anaemia and myocarditis, he was found to have achlorhydria with no excess of mucus in any fraction of the test meal. Directly he was given hydrochloric acid the diarrhoea stopped. He was repeatedly transfused and his very septic tonsils were enucleated. He recovered completely from the anaemia and myocarditis, and has had no return of symptoms, but he still (August 1931) continues to take acid. During the last two years he has also taken liver, but this has not had any material effect on the condition of his blood.

In the *Guy's Hospital Reports* for 1927 there is a microphotograph of the pyloric end of the stomach of a woman of 61, who died under my care in 1926 of subacute combined degeneration of the cord after a year's illness. It shows an extreme degree of atrophy of the mucous membrane compared with the normal; two other microphotographs show how the submucous tissue is infiltrated with masses of streptococci. She had had no gastric symptoms, but complete achlorhydria, and though her blood-picture was typical of Addison's anaemia, the haemoglobin was still 60 per cent. two days before she died. This case, which was recorded by Waterfield, is I believe, the only one in which atrophic gastritis has been demonstrated in subacute combined degeneration of the cord.

In some cases of simple achlorhydric anaemia the history strongly suggests that the achlorhydria is the result of atrophic gastritis.

In a woman of 48 under my care, whose case has been recorded by Witts, simple achlorhydric anaemia, with 31 per cent. haemoglobin and 3,808,000 red corpuscles per c.mm. (colour index 0.4), followed oxalic acid poisoning, which must have caused atrophic gastritis and achylia.

(iii) *Total gastrectomy.* Total gastrectomy has only rarely been performed, and the mortality is very high. If it were true, as Castle concluded from his investigations, that the stomach normally secretes something, possibly an enzyme, which reacts with protein in neutral solution to produce a material, which is *essential* for the full activity of the bone-marrow, then Addison's anaemia would always develop after the operation. This does in fact sometimes occur. Thus Hartman (1921) recorded the case of a man of 58, on whom W. J. Mayo had performed total gastrectomy for carcinoma, at a time when his blood was quite normal; after being well for a year he developed typical Addison's anaemia from which he died $3\frac{3}{4}$ years after the operation. It has been generally assumed that Moynihan's patient, who died in 1911 from severe anaemia of less than a year's duration $3\frac{3}{4}$ years after complete gastrectomy for cancer without anything abnormal being found *post mortem*, must have had Addison's anaemia. As no blood examination was made, it is at least equally probable that the anaemia was of the simple achlorhydric variety. The bone-marrow was not examined *post mortem*, and the pathologist tells me that there was no recognizable naked-eye siderosis of the liver, and he thinks it very probable that the anaemia was not Addisonian.

On the other hand, total gastrectomy appears to be compatible with good health. Thus a man on whom Butler performed complete gastrectomy for a large non-malignant ulcer in 1926 is still perfectly well; he has no anaemia, his haemoglobin being 85 per cent. and his red corpuscles numbering 4,980,000 per c.mm. on July 31, 1931. The only treatment he has had has been the regular administration of dilute hydrochloric acid and pepsin.

A man with complete achylia following total gastrectomy is, however, never safe: a case recorded by Ellis shows that subacute combined degeneration and Addison's anaemia may develop as long as seventeen years after the performance of the operation. Dennig has also published the case of a man of 41, who developed typical Addison's anaemia and subacute combined degeneration with glossitis eight years after total gastrectomy for gastric ulcer. After temporary improvement with liver he died of bronchopneumonia; *post mortem* characteristic changes were found in the bone-marrow and spinal cord. Hochrein recorded the case of a man of 55 who developed Addison's anaemia eight years after complete resection of the stomach for carcinoma; he improved very quickly with liver. Lastly, a woman of 51, on whom Breitenbach performed complete gastrectomy for carcinoma, developed Addison's anaemia $6\frac{1}{2}$ years later. The long latent period in these cases suggests that the achylia predisposes to the development of Addison's anaemia and subacute combined degeneration in some more subtle manner than by simply depriving the bone-marrow of an essential hormone.

B. *Achlorhydria without achylia.* Achlorhydria may also occur in spite of the fact that the gastric mucous membrane is still capable of secreting hydrochloric acid.

(i) *Chronic, non-atrophic, gastritis.* In this condition the mucous membrane will again secrete hydrochloric acid if recovery from the gastritis occurs either spontaneously, which is very rare, or as a result of treatment. For several years all my cases of chronic gastritis have, whenever possible, been treated by removal of the exciting cause, an unirritating diet, and daily lavage with dilute hydrogen peroxide, with the result that free hydrochloric acid has frequently reappeared. In the large majority of such cases excess of mucus was present in every fraction of the original test meal; it forms a tenacious covering over the surface of the mucous membrane, which actually blocks the mouths of the glands and prevents their secretion from gaining access to the lumen of the stomach, and small quantities of free acid which escape are neutralized by the weakly alkaline mucus. It is thus generally possible to recognize at once which cases of achlorhydria are capable of recovery, as free hydrochloric acid is often found in a second test meal given after the mucus has been dislodged by preliminary lavage with water. In rare cases, however, we have found that the usual treatment of gastritis has led to the return of free hydrochloric acid, even when the absence of mucus from the test meal has led to the supposition that the achlorhydria was the result of true achylia. In such cases the absence of

secretion must have been due to the damaged, but not irreparable, condition of the secreting cells.

A Rehfuß test meal often reveals the presence of free hydrochloric acid in one or more fractions in cases in which complete achlorhydria would have been found with the old one-hour test breakfast of Ewald and Boas. During the last six months we have systematically removed additional fractions after all food has left the stomach. This is chiefly of value as a measure of hypersecretion, but in one case, which would otherwise have been regarded as complete achlorhydria, a considerable quantity of free hydrochloric acid appeared in the two additional fractions. This is a further reason for making this modification in the standard test meal, as it at once indicates that the achlorhydria is only apparent.

Histamine injections. We have injected histamine in a considerable number of cases of achlorhydria, but have found it of no diagnostic value, as it calls forth secretion of acid only when the achlorhydria is due to chronic non-atrophic gastritis and therefore curable by treatment. On the other hand, in several instances it has led to no secretion of acid, although treatment has led to the reappearance of normal secretion. It is clear, therefore, that every case of achlorhydria which may conceivably be caused by gastritis should be treated, and there is consequently no need to try first the effect of histamine, the injection of which may occasionally produce unpleasant symptoms. If, however, a second test meal is to be given, it is obvious that the effect of preliminary lavage should be tried rather than that of an injection of histamine, as success with the former is a guarantee that normal secretion will be restored by treatment.

Causes of chronic gastritis. Chronic gastritis may be a sequel of acute gastritis or it may be chronic throughout.

(a) Many cases of acute indigestion, generally regarded as purely functional, are really the result of acute gastritis, which may be followed by more or less permanent chronic gastritis, which often remains completely latent. The two common causes are direct irritation in acute food poisoning, especially when associated with severe epigastric pain and vomiting, and haematogenous irritation in acute infections. Faber has shown the great importance of the latter, and also of such chronic infections as tuberculosis. I am convinced that the abdominal symptoms of so-called gastric influenza are caused by acute gastritis, as I have seen several cases of chronic gastritis with achlorhydria which dated from an attack of this kind.

(b) The commonest cause of primary chronic gastritis is over-indulgence in alcohol. In addition to the familiar types of people who drink too much, I have seen a good many cases since the War among the 'bright young people' who frequent cocktail-parties. Excessive smoking and the bolting of food are also common causes. I believe that these exciting causes can only affect about 20 per cent. of people: the remaining 80 per cent. have a gastric secretion within the limits generally regarded as 'normal' and are thus sufficiently protected by the diluting and antiseptic action of their

gastric juice. I will not now refer to the 10 per cent. with constitutional hyperchlorhydria, but the 10 per cent. with constitutional hypochlorhydria, including the 1 or 2 per cent. with achylia, will certainly develop chronic gastritis under these conditions, and when the gastritis has led to achlorhydria it will be further aggravated by secondary infection with streptococci swallowed in the secretions from pyorrhoea alveolaris and from inflamed tonsils and nasal sinuses.

The chronic gastritis of Addison's anaemia and subacute combined degeneration of the cord. I have already referred to Faber's post-mortem investigations, which showed that every stage of chronic gastritis may be found in association with Addison's anaemia. Passey examined a fragment of mucous membrane removed during an operation for appendicitis on two patients of mine with achlorhydria, one of whom had Addison's anaemia and the other no anaemia. There was definite inflammation without any atrophy in both, and the oxyntic cells were normal in number. Free hydrochloric acid subsequently appeared in the stomach of the non-anaemic patient.

When there is a definite history of food poisoning or other possible cause of gastritis and excess of mucus is present in each fraction of a test meal, the achlorhydria may be due to a recoverable form of chronic gastritis. Thus one man developed Addison's anaemia two years after a severe attack of abdominal pain, vomiting, and diarrhoea after eating oysters; another developed subacute combined degeneration after a period of indigestion, which had begun six months before after an attack of severe diarrhoea ascribed to ptomaine poisoning. It is, however, only possible to ascribe the achlorhydria in Addison's anaemia and subacute combined degeneration of the cord to chronic gastritis with certainty when the secretion of free acid returns as a result of treatment. I have seen four such cases, but, so far as I know, no others have been recorded. An account of the first was published by Shaw in 1926, and the second by myself in 1931; the third and fourth were similar to the second, but the symptoms of subacute combined degeneration were more prominent than those caused by the anaemia, and only a very small quantity of free hydrochloric acid was present when the second test meal was given.

Addison's anaemia following achlorhydria due to alcoholic and dental gastritis; recovery from Addison's anaemia (eight years) and return of secretion of hydrochloric acid without administration of liver. The patient served in the East during the War, and in 1920, when 31 years old, had repeated attacks of diarrhoea whilst on duty in Constantinople. He then became progressively more pale, and complained of soreness of the tongue. He was invalided home in 1921, and soon developed attacks of vomiting with loss of strength and shortness of breath. On admission to Millbank in October 1921, his haemoglobin was 20 per cent. and red corpuscles 740,000 per c.mm. with a few megaloblasts, and white cells 4,000 per c.mm. He was admitted under me in January 1923, having been transfused eight times. He had a lemon-yellow colour and atrophic glossitis. His haemoglobin percentage was 42 and red corpuscles numbered 1,670,000 c.mm. (colour index 1.26);

the Price-Jones (cell-diameter) curve was typical of Addison's anaemia and his blood gave a positive indirect van den Bergh reaction. He was given hydrochloric acid, and his teeth, which had infected roots, though there was no pyorrhoea, were extracted. He soon began to improve, and in July his haemoglobin was 75 per cent. He was then able to return to his old occupation of schoolmaster, and he has continued without any return of anaemia to the present time. His haemoglobin was 110 per cent. in October 1923, and has been over 100 per cent., and the red corpuscles over 5,000,000 per c.mm. each time his blood has been examined; the van den Bergh has always been negative. He has never had liver. *He continued to take hydrochloric acid until October 1925, when he complained of gastric symptoms and was found to have a high normal curve of acidity. He therefore discontinued the acid.*

In this case the chronic gastritis was probably alcoholic in origin, and recovery occurred when the patient became teetotal. I have seen two other cases of Addison's anaemia, and Roth has observed another, in which the achlorhydria was probably due to chronic alcoholic gastritis, as cirrhosis was also present.

Addison's anaemia with achlorhydria due to gastritis; recovery from anaemia with liver and restoration of gastric secretion with lavage. A man of 70 had an attack of severe diarrhoea in 1890, after which he suffered from flatulent dyspepsia. At the end of 1929 he became short of breath and his tongue was sore. In January 1930 he had typical Addison's anaemia with a positive indirect van den Bergh reaction, atrophic glossitis, slight splenomegaly, and complete achlorhydria with excess of mucus in each fraction. He was given liver, gastric lavage with hydrogen peroxide, and his pyorrhoea was treated. On April 2 his blood was normal, and a test meal showed a normal secretion of hydrochloric acid.

Campbell and Conybeare, in their analysis of Guy's Hospital cases of Addison's anaemia, record that of a woman of 42, who had the typical blood-picture with 20 per cent. haemoglobin. Unfortunately she was not given a test meal, but when they saw her seven years later her haemoglobin percentage was 84, and a test meal gave a normal curve of acidity. This is probably another example of the restoration of gastric secretion in a case of Addison's anaemia, in which the achlorhydria was due to gastritis, but in the absence of a test meal on her first admission this must of course remain unproved.

It has generally been assumed that the persistence of achlorhydria after recovery from Addison's anaemia with liver treatment is evidence that the former is caused by some permanent condition. I have no doubt, however, that if all those cases in which the achlorhydria is non-familial and appears to be due to gastritis had treatment given for the gastritis and not merely for the anaemia, many would be added to my four in which the secretion of acid returned.

The history, gastric analysis, and response to histamine injections and lavage show that the achlorhydria in the majority of cases of simple achlorhydric anaemia is a result of chronic gastritis. Thus Davies found excess of mucus in the gastric contents in eleven out of fifteen cases; in four

of these free hydrochloric acid was secreted after injection of histamine, and in two others there was a fall in pH, though no free acid appeared.

(ii) *The achlorhydria of carcinoma of the stomach.* Complete achlorhydria was found in 50 per cent. of cases collected from the Mayo Clinic by Hartman (1921), and in 65 per cent. of seventy-four cases at Guy's Hospital and New Lodge Clinic. It has always been assumed that the achlorhydria is a result of the carcinoma, although none of the numerous theories which have been proposed to explain its occurrence appeared to be satisfactory. In 1929 in my Schorstein Lecture I gave reasons for believing that this assumption is unjustified, and that the achlorhydria is a result of chronic gastritis, which precedes the onset of the carcinoma and is in fact the most common predisposing condition of the latter. I have never seen a case of carcinoma in which free hydrochloric acid was present at an early stage and disappeared as the disease advanced, and I have been unable to discover any record of such a case. On the other hand, I have seen three cases of gastric ulcer in which a test meal was given both before and after the onset of malignant degeneration: in each case the acidity, which was high in two and normal in one, was undiminished when the carcinoma had developed. Pollard and Bloomfield have recently recorded two cases of carcinoma of the stomach, in which there was a definite increase in the quantity of free acid present when a second test meal was given after intervals of four and six months respectively.

In the few cases in which a test meal has been given before as well as after the development of carcinoma of the stomach associated with achlorhydria, achlorhydria was already present on the first occasion.

Achlorhydria preceding the development of carcinoma of the stomach. In April 1924 I saw a man of 51 who gave a history of periodic attacks of epigastric discomfort for fifteen years, which he ascribed to excessive smoking. The X-rays showed a spasmodic condition of the pyloric vestibule but no filling defect. There was complete achlorhydria with much excess of mucus. Though the possibility of carcinoma was considered, this seemed to be excluded by the complete disappearance of symptoms on taking hydrochloric acid and giving up smoking. He gained a stone and a quarter in weight, and remained completely free from symptoms till September 1925, when he began smoking again and discontinued taking acid. In January 1926 he returned to the Clinic, having lost nearly a stone in weight. The X-rays now showed a definite filling defect in the pyloric part of the stomach, blood was present in every fraction of the test meal, which still showed achlorhydria, and the stools contained much occult blood. Carcinoma was diagnosed and partial gastrectomy performed. He survived till July 1930.

The good health and gain in weight between the patient's two visits to the Clinic make it doubtful whether anything more than chronic gastritis could have been present on the first occasion, but, even if a very early growth was already present in April 1924, the achlorhydria must at that date have been a result of chronic gastritis and not of carcinoma.

Alexander has recorded the case of a man of 47, who gave a two years'

history of epigastric discomfort and nausea; he had achlorhydria and improved with hydrochloric acid, but twenty-six months later severe pain developed, and he was then found to have an inoperable growth of the stomach. A woman of 62, who complained of fullness and burning after meals was seen by Dr. R. A. Veale in June 1926; she had achlorhydria with excess of mucus. Two years later pain and anorexia developed, and in February 1929 achlorhydria was again present, and an inoperable carcinoma of the pyloric end of the stomach was found on exploration. Porges states that he has seen cases in which achlorhydria was found to be present many years before the appearance of symptoms of carcinoma.

In a large proportion of cases of carcinoma of the stomach, which show unmistakable pathological evidence of being secondary to a chronic ulcer, free hydrochloric acid is found. Free acid was present in my three cases referred to above, and in all of Stewart's nine ulcer-cancer cases in which a fractional test meal was given. In twelve out of fourteen operative cases of definite ulcer-cancer described by Orator free hydrochloric acid was found with an Ewald test meal; it is not unlikely that a fractional test meal would have revealed the presence of free acid in one or more fractions in the two remaining cases. On the other hand, achlorhydria was found in twenty-two out of thirty of Stewart's cases and in seven out of eight of Orator's, in which the carcinoma appeared to be 'primary'.

TABLE III. *Length of History in 24 New Lodge Clinic and 14 Guy's Hospital cases of Carcinoma of the Stomach.*

No. of Cases.	Free HCl in Fractional Test meal.	Less than 6 months.	6-18 months.	18 months and over.	Average (excluding*).
14	Present	2 (5/12; 6/12)	2 (10/12; 12/12)	10 (1½, 1½, 1½, 2½, 3½, 4, 4, 12, 12, 12, 30* years)	3 years
24	Absent	17	6	1 (20 years*)	9 months

Using a fractional test meal, free hydrochloric acid was found in all but one of eleven Guy's Hospital and New Lodge Clinic cases of carcinoma of the stomach with more than eighteen months' history, whereas seventeen out of nineteen with a history of less than six months had achlorhydria (Table III). Most of the former were presumably cases of ulcer-cancer and of the latter 'primary' cancer. In 1911 Panton and Tidy had obtained similar results with the less accurate Ewald test meal; they found that twenty out of twenty-five cases with a history of nine months or less had achlorhydria, whereas four out of five with a history of more than two years had free acid present. Stewart found that the average duration of symptoms in seventeen cases of definite ulcer-cancer was 5½ years, or only 2½ years less than the average duration of symptoms in a contemporary series of 218 cases of simple gastric ulcer, whereas in sixty-nine cases of 'primary' cancer it was eleven months, and in ten out of Orator's sixteen cases of ulcer-cancer

symptoms had been present for periods varying between 1 and 28 years, whereas in five out of seven cases of 'primary' cancer there was less than a year's history. It seems clear, therefore, that when free acid is present the carcinoma is likely to be secondary to ulcer, and when achlorhydria is present it is generally secondary to gastritis. Thus achlorhydria is not a sign of advanced carcinoma, in the early stage of which free acid was present, as the duration of symptoms would then tend to be considerably shorter when free acid is present than in cases with achlorhydria, whereas the reverse is actually the case.

It is natural that there should be exceptions to the general rule as to the association of free acid with ulcer-cancer and achlorhydria with gastritis-cancer, and to the relative duration of symptoms in cases with free acid and with achlorhydria. Thus achlorhydria may very exceptionally occur in very chronic cases of ulcer owing to secondary gastritis, and gastritis does not invariably lead to the complete disappearance of free acid from the gastric contents. Moreover, gastric ulcers are occasionally latent for long periods, and chronic gastritis, though generally latent, sometimes gives rise to definite gastric symptoms.

If achlorhydria were a result of the development of carcinoma in a stomach which had previously secreted a normal gastric juice, the prospect of survival after operation would be considerably better in those cases in which free acid was present than in those with achlorhydria. This, however, is not the case, as on analysing the results of operation five years after gastrectomy had been performed for cancer of the stomach, Hartman (1921) found that 44 per cent. of 39 patients who had had complete achlorhydria were still alive, compared with only 22 per cent. of 41 with free hydrochloric acid. These figures strongly support the view that achlorhydria precedes the development of carcinoma and is not its cause.

During the last few years a number of German pathologists have made a special study of the whole of the mucous membrane of specimens obtained by very extensive, though generally incomplete, gastrectomy performed for chronic ulcer and carcinoma. They have shown that in all cases of carcinoma gastritis is present. In those cases in which it appears to be 'primary', well-marked atrophic gastritis is present throughout the stomach, whether the growth is small or widespread. Thus Orator found diffuse, generally atrophic gastritis involving the fundus as well as the pyloric region in nineteen out of twenty such cases; in the remaining case, one of pyloric cancer, there was a very long history of alcoholic gastritis, but most of the mucous membrane of the fundus, though slightly inflamed, was not atrophic. On the other hand, although there was well-marked gastritis in the pyloric region in each of his eight cases of definite ulcer-cancer, in five the mucous membrane of the fundus was perfectly healthy, in two it showed slight gastritis, and in only one was severe gastritis present. Konjetzny, Faber, and others have shown that more or less localized gastritis is present in all or almost all cases of chronic ulcer, which explains its association with

ulcer-cancer. This makes the presence of universal atrophic gastritis in cases of so-called 'primary' carcinoma all the more significant. It seems clear, in fact, from the clinical and pathological evidence that the carcinoma is no more primary than in the ulcer-cancer cases, but is secondary to the gastritis, so that this form of cancer of the stomach should be called gastritis-cancer in contrast with ulcer-cancer, which is due to malignant degeneration of a simple ulcer.

Addison's anaemia and subacute combined degeneration of the cord in carcinoma of the stomach. I have seen five cases of typical Addison's anaemia, two of which were accompanied by subacute combined degeneration of the spinal cord, associated with cancer of the stomach, and several similar cases have been recorded. In commenting on the first of my cases, which was reported by Waterfield in 1923, I suggested that the nervous symptoms and anaemia were a result of the achlorhydria, to which the carcinoma had given rise, although weakness and paraesthesia of the hands and feet were present for two months before any gastric symptoms had developed and a year before carcinoma was discovered at an exploratory operation. I now realize that the carcinoma was probably secondary to chronic gastritis, and that the subacute combined degeneration of the spinal cord and anaemia resulted from the achlorhydria which was present before the carcinoma developed. This was clearly the sequence of events in a case mentioned by Porges, in which a small, non-ulcerated carcinoma of the stomach, no larger than a pea, which had given rise to no symptoms, was found at the autopsy of a patient who had died of Addison's anaemia.

Simpson recently made repeated observations on the blood in a case at Guy's Hospital, in which symptoms and signs of Addison's anaemia and subacute combined degeneration of the spinal cord developed simultaneously with those of carcinoma of the stomach. Treatment with hog's stomach led to a typical reticulocytic crisis; the haemoglobin percentage and red corpuscles rose from 36 to 62 per cent. and from 1,240,000 to 2,340,000 per c.mm. respectively, the colour index fell from 1.5 to 1.3, and the indirect van den Bergh, which had been positive, became negative. Complete achlorhydria was present. An inoperable carcinoma of the stomach was found at operation. At the autopsy three months later the typical macroscopical and microscopical changes associated with Addison's anaemia and subacute combined degeneration were present in the bone-marrow, liver, spleen, and spinal cord.

In the following case carcinoma only developed after the patient had been apparently cured of Addison's anaemia by liver treatment. It will be interesting to note in the future whether the incidence of carcinoma of the stomach is greater among patients who have recovered from Addison's anaemia and still have achlorhydria and gastritis than among the general public.

Carcinoma of the stomach developing in a patient nine years after onset of Addison's anaemia and four years after symptomatic cure. An inn-keeper

developed symptoms of anaemia when aged 54 in 1922. In January 1923 he was found to have achlorhydria. In December 1926 he was in Guy's Hospital under my care with typical Addison's anaemia, his haemoglobin percentage being 30 and his red cells numbering only 725,000 per c.mm. The van den Bergh test gave a positive indirect reaction and a negative direct reaction. He had complete achlorhydria; the X-rays showed no abnormality in his stomach. He was transfused three times and given liver and hydrochloric acid. By February 1927 his haemoglobin percentage had risen to 85 and his red cells to 4,200,000 per c.mm. He continued to take acid and liver and felt perfectly well when he returned to hospital in July 1931 on account of glands in his neck. These proved to be tuberculous. Though he had no abdominal symptoms, the X-rays showed that he had a filling defect in the pyloric end of his stomach, and occult blood was present in the stools. He still had achlorhydria, but was not anaemic: he had 94 per cent. haemoglobin and 4,720,000 red corpuscles per c.mm. with no megalocytes and normal leucocytes. Partial gastrectomy was performed; microscopical examination showed that the tumour was an atrophic scirrhus carcinoma; the mucous membrane of the unaffected part of the stomach showed atrophy and cystic degeneration of the glands. The patient died a week later with acute maniacal symptoms. At the autopsy the wound was healthy, no secondary deposits were found, and the bone-marrow appeared to be normal, but the liver and kidneys gave a positive Perl reaction.

As gastritis is a common complication of constitutional achylia gastrica (*vide supra*), it is natural that carcinoma of the stomach and Addison's anaemia should sometimes occur in different members of the same family. Thus Borovanská-Felklová records the history of five brothers, four of whom had achylia; three of the latter had typical Addison's anaemia, and the fourth, though not anaemic, had a colour index of 1.13. Their father had died of cancer of the stomach, and at the autopsy on the eldest son, who had died of Addison's anaemia, a latent carcinoma of the stomach was discovered.

Simple achlorhydric anaemia and carcinoma of the stomach. In the following case carcinoma of the stomach appears to have been secondary to chronic gastritis, which had already caused simple achlorhydric anaemia.

Carcinoma of the stomach developing in a woman with simple achlorhydric anaemia secondary to gastritis. Mrs. R., aged 61, was admitted in May 1930 with a history that she had been unwell for five years. She had first consulted her doctor in 1927 on account of general weakness and dyspnoea, which he attributed to severe anaemia, as she was very pale. In July 1928 she was found to have only 35 per cent. haemoglobin with 3,580,000 red corpuscles per c.mm.; no occult blood was present in her stools. The anaemia persisted in spite of treatment with iron and arsenic injections and liver extract, and she had occasional indigestion.

On admission there was an ill-defined tender tumour in the epigastrium. The blood-count was almost identical with that of two years before, the haemoglobin percentage being 36 and the red cells numbering 3,500,000 per c.mm. The white cells numbered 7,800 per c.mm. with a normal differential count. The van den Bergh reaction was negative. A test meal showed

complete achlorhydria. A large filling defect of the pyloric and of the stomach was found with the X-rays. The Wassermann reaction was negative.

The patient was given 40 and subsequently 60 gr. of iron and ammonium citrate three times a day and was transfused three times. Her haemoglobin had risen to 66 per cent. by June 12, 1930, when partial gastrectomy was performed for a mass involving the pyloric end of the stomach. She made an uninterrupted recovery, and by July 23 her haemoglobin had risen to 90 per cent. and her red corpuscles to 4,700,000 per c.mm., the colour index having thus risen from 0.5 in June 1928 to 0.95 in July 1930.

Histological examination showed the presence of a primary carcinoma with secondary peptic ulceration. The rest of the gastric mucosa was the seat of advanced chronic gastritis, mainly hypertrophic, but with atrophic changes in the lesser curvature region above the growth. Unmistakable tubercle follicles with characteristic giant cells in the subserous and muscular coats over part of the growth were discovered, together with an early tuberculous lesion in one of the lymph glands of the lesser curvature. The lymph glands along both curvatures were extensively invaded by carcinoma.

It is very unlikely that the tumour had been in existence for more than two years, so that the anaemia, which had probably been present for four years and was certainly as severe two years before as at the time of the operation, must have been of the simple achlorhydric type and not a result of the growth.

Complete achlorhydria was still present after the operation. There was thus just as much reason for anaemia to develop now as four years ago. The patient was therefore advised to take 40 gr. of iron and ammonium citrate three times a day after meals for the rest of her life. When seen in October 1931 her haemoglobin percentage was 78 and her red corpuscles numbered 4,500,000 per c.mm.

(iii) *Achlorhydria following gastro-jejunostomy.* The gastric acidity is lowered after gastro-jejunostomy owing to the entrance of the alkaline juices of the duodenum from the afferent loop of the jejunum into the stomach, and to a less extent to the increased rapidity of evacuation. As the operation is most frequently performed for duodenal ulcer, in which hyperchlorhydria is present, complete neutralization does not often occur, because the secretion of a very acid juice, being constitutional and not a result of the ulcer, persists. When achlorhydria is found after gastro-jejunostomy, it is generally due to the operation having been performed for some condition other than duodenal ulcer, in which case it may have been already present before the operation. If, however, achlorhydria follows an operation for ulcer, it is obvious that it is not the result of achylia, but of neutralization of the acid secreted by the gastric mucous membrane with the alkaline duodenal juice.

Addison's anaemia developed eight years after gastro-jejunostomy for a lesser curvature ulcer in a case recorded by Conybeare, and in unpublished cases of Willcox, Houston, Horder, and Langdon-Brown. I have seen a case of typical subacute combined degeneration of the spinal cord without anaemia develop in a woman of 52 fourteen years after a gastro-jejunostomy had been performed for a supposed ulcer. As she had also a good deal of abdominal pain due to partial obstruction of the jejunum, the gastro-jejunostomy was

undone on my advice. It was then found that she still had achlorhydria, which was presumably the result of constitutional achylia, as her father had died of Addison's anaemia. No scar of a healed ulcer was found at the second operation, and the original dyspeptic symptoms for which the gastro-jejunostomy was performed were probably due to the achlorhydria. The abdominal pain resulting from the gastro-jejunostomy disappeared when it was undone, and it was now possible to give large doses of hydrochloric acid, with which treatment there has been no return of dyspepsia, and the spinal symptoms have become much less severe. The following case, which I recently published with Glanvill, is the only one, so far as I know, in which a test meal had been given before the operation, so that absolute proof was present that the achlorhydria was due simply to neutralization of acid and not to achylia.

Addison's anaemia and subacute combined degeneration of the spinal cord with achlorhydria resulting from gastro-jejunostomy performed for gastric ulcer. A man of 34 had a gastro-jejunostomy performed in May 1927 for a large lesser curvature gastric ulcer, a test meal having shown the presence of free hydrochloric acid. Six months later diarrhoea developed, and in November 1929 he became breathless and soon afterwards complained of weakness and then numbness and tingling of his legs. In March 1930 he was found to have the typical blood-picture of Addison's anaemia (red corpuscles 1,680,000 per c.mm., haemoglobin 44 per cent., colour index 1.28, megalocytosis, indirect positive van den Bergh reaction), atrophic glossitis, lost ankle-jerks, and complete achlorhydria. He was given liver and hydrochloric acid, but took very little of the former after he left the hospital. He quickly recovered, the blood becoming perfectly normal with 95 per cent. haemoglobin by May, but achlorhydria was still present. The ankle-jerks were still absent in September, though the paraesthesia had disappeared.

Neutralization of the acid following gastro-jejunostomy may also give rise to severe non-Addisonian anaemia, as in the following case, which I published at the same time with Cosin. No test meal was given before the gastro-jejunostomy, but there must have been free acid, as the perforation showed that an active ulcer had been present.

Simple achlorhydric anaemia resulting from gastro-jejunostomy performed for duodenal ulcer. A man of 53 had a perforated 'pyloric' ulcer sutured in 1910 and a gastro-jejunostomy performed for pyloric stenosis the following year. He remained well until 1926, when he developed diarrhoea. He gradually became more ill, and in July 1930 his haemoglobin percentage was 27 and red corpuscles numbered 2,600,000 per c.mm., the colour index being 0.5 and average diameter of the cells only 6.9μ . He did not improve with liver, but large doses of iron with hydrochloric acid led to a reticulocytic reaction and rapid recovery, and in October his haemoglobin was 98 per cent. and red-cell count 5,030,000 per c.mm.

Witts has recorded four female cases and Davies five female and one male case of simple achlorhydric anaemia, with haemoglobin varying between 24 and 70 per cent., occurring between four and twenty years after gastro-jejunostomy; all responded to iron treatment.

In 1931 a woman of 58 was under my care with 18 per cent. haemoglobin and 1,420,000 red corpuscles per c.mm. ; achlorhydria had followed a gastro-jejunosomy performed for a prepyloric ulcer in 1920. She improved rapidly with large doses of iron, but an acute cerebral attack developed after she had been having 160 gr. of iron a day for three weeks. I believe this was due to iron poisoning, the symptoms being exactly similar to those of severe lead encephalopathy. She made a complete recovery, and six months later had 101 per cent. haemoglobin and 5,300,000 red corpuscles per c.mm.

Achlorhydria following partial gastrectomy. Partial gastrectomy owes its reputation of being the only satisfactory surgical treatment of gastric ulcer to the fact that it is generally followed by achlorhydria if a sufficiently large part of the stomach has been removed, and that a new ulcer in the remaining portion of the stomach or in the jejunum cannot develop in the absence of free hydrochloric acid. In the few cases in which a new ulcer forms after partial gastrectomy, free hydrochloric acid is almost always found. The achlorhydria commonly produced by the operation is not due to achylia, as the part of the stomach still present is that which normally secretes the greater part of the acid. Thorough admixture and consequent neutralization with the alkaline duodenal juices and rapid drainage account for the achlorhydria. It is often possible to show by special means that acid is still being secreted: thus, if care is taken to introduce the tube only just beyond the cardia and no meal is given, free acid may appear as a result of psychic secretion on showing the hungry patient appetizing food or on injecting histamine; in other cases free acid may appear after an Ewald test meal or a meat meal, though none appears with the ordinary fractional test meal of gruel.

In 44 per cent. of fifty-two cases, in which Taylor had performed partial gastrectomy, simple achlorhydric anaemia was present; its incidence was greater in women than men, and in spite of the low haemoglobin percentage there were generally no symptoms of anaemia. On the other hand, anaemia was only present in three out of seventy-seven patients on whom Henschen had performed partial gastrectomy for ulcer between 1920 and 1930, and these were found to be suffering from menorrhagia, carcinoma of the cervix, and phthisis respectively. He does not, however, state what proportion of his cases had achlorhydria, a point of great importance, as so long as free hydrochloric acid is present, there appears to be no tendency for anaemia to develop.

Though simple achlorhydric anaemia is quite common after partial gastrectomy, Addison's anaemia is rare. The following five cases are the only ones of the kind which I have been able to discover.

Five years after partial gastrectomy for a gastric ulcer a woman of 43 developed indigestion; she had achlorhydria and a year later symptoms of anaemia. Eight months after this her haemoglobin percentage was 17 and her red corpuscles 662,000 per c.mm.; she died after a transfusion (Delore, 1928).

Six years after partial gastrectomy for a chronic ulcer very severe and typical Addison's anaemia developed in a man of 50: the haemoglobin percentage was 22 and the red cells numbered 630,000 per c.mm., the colour index being 1.8. There was complete achlorhydria, the spleen was enlarged, and glossitis was present. The patient recovered on being given liver (Scheidel, 1930).

Henschen quotes a case of Rindfleisch, in which Addison's anaemia followed partial gastrectomy, but no details are given.

Enderlin refers to a case of his own in which Addison's anaemia followed a complete gastrectomy, but gives no details (1930).

Mr. H. B. Butler tells me that a woman on whom he had performed partial gastrectomy for hour-glass stomach died two years later of severe anaemia, which was said to be Addisonian.

Relation of Addison's Anaemia to Simple Achlorhydric Anaemia

In view of the fact that both Addison's anaemia and simple achlorhydric anaemia can develop from achlorhydria of every kind, although the former is more common with complete achylia and the latter when there is no permanent inability of the gastric mucous membrane to secrete acid, it is natural that cases in which an intermediate type of anaemia showing some of the features of both should occasionally develop, and that simple achlorhydric anaemia should sometimes precede the development of Addison's anaemia. These possibilities have been fully discussed by Witts. He described two cases and referred to one of Zadek's of an intermediate type of anaemia associated with achlorhydria, in which megaloblasts were present and the van den Bergh test gave an indirect positive reaction, but the colour index was low and the Price-Jones curve normal. He pointed out, however, that such cases are rare, and that both simple achlorhydric anaemia and Addison's anaemia are generally true to type from the onset.

Witts also recorded a remarkable case in which simple achlorhydric anaemia was present for six years before Addison's anaemia with subacute combined degeneration of the spinal cord developed; this is the patient already referred to whose sister and two aunts had died of Addison's anaemia. A similar sequence of events occurred in the patient of Gram's, who is mentioned above in connexion with the occurrence of both types of anaemia in different members of a family affected with constitutional achylia gastrica. Hochrein's patient, to whom I have already referred in connexion with the development of Addison's anaemia after complete gastrectomy, improved rapidly with liver treatment, but Morawitz has since reported that four months later he developed severe secondary anaemia which was uninfluenced by liver; in this case the more usual sequence of Addison's anaemia following simple achlorhydric anaemia was reversed.

Summary

1. Achlorhydria, or the absence of free hydrochloric acid from any fraction of a test meal, may be due to the following causes:

A. *Achylia gastrica* :

i. Constitutional achylia gastrica, a familial condition depending upon an inborn error of secretion.

ii. Atrophic gastritis.

iii. Total gastrectomy.

B. *Achlorhydria without achylia* :

i. Chronic, non-atrophic, gastritis, in which free acid may return as a result of treatment. This is also the cause of the achlorhydria of carcinoma of the stomach, the gastritis and achlorhydria preceding the development of the carcinoma.

ii. Gastro-jejunostomy.

iii. Partial gastrectomy.

2. The achlorhydria which is an essential predisposing cause of about 99 per cent. of cases of Addison's anaemia and subacute combined degeneration of the spinal cord may be a result of any of the causes mentioned above, but the likelihood of one or both developing is considerably greater when the achlorhydria is due to achylia gastrica than when the mucous membrane is still capable of secreting free hydrochloric acid.

3. The achlorhydria, which gives rise to a non-Addisonian or simple form of anaemia, may also result from any of the above causes, but in contrast with Addison's anaemia it is most likely to develop in those varieties of achlorhydria which are not caused by achylia.

4. As both forms of anaemia may develop from each variety of achlorhydria, it is natural that the simple anaemias should sometimes develop after a period of years into Addison's anaemia, and that in constitutional familial achylia the two different forms of anaemia should occasionally be present in different members of the same family.

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CRITICAL REVIEW¹THE DIAGNOSIS AND TREATMENT OF SYPHILIS OF
THE AORTA AND HEART

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THE subject of this review has excited of late an interest which appears to be increasing, if the number of papers devoted to its discussion be a reliable criterion. For example, the whole of a recent number of the *American Heart Journal* was occupied by a series of papers setting forth different aspects of this subject. It is not a matter for wonder or surprise that this should be so. Syphilis itself has been subjected to a fierce and calculated attack during the past two or three decades, an attack instigated as well as guided by the new knowledge of this infection that was garnered in the early years of the present century. It is difficult to realize that thirty years ago we did not know that syphilis was a spirochaetal infection; that Wassermann's application of the complement fixation hypothesis had not yet been attempted, since the hypothesis itself was only then being stated by Ehrlich; and that chemotherapy of the kind to which syphilis is now universally subjected had not even attained to those early experiments with atoxyl in the treatment of trypanosomiasis which opened this chapter of therapeutics.

Now all these additions to our knowledge of syphilis found, in the early part of this century, a field prepared for their application. The incidence of syphilis was multiplied manifold by the European War—an aspect of this war as sordid as it has been constant in all modern campaigns—and the demand for new knowledge would have been urgent and insistent even if that knowledge had not already existed. Moreover, the collectivist machinery which the war also fostered made it easy to inaugurate a vigorous campaign of early diagnosis and treatment.

The Incidence of Cardiovascular Syphilis

In spite of all this, however, the medical profession was slow in recognizing the fact that its cardio-aortic phenomena are among the most formidable achievements of this infection; formidable both because it is a vital structure that is attacked, and also because the attack is so persistent and

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inexpugnable. Those writers—Welch, Döhle, Heller, and others—who, in the nineteenth century, insisted on the syphilitic nature of these aortic lesions were apparently not listened to at first. It is, for example, significant that in a deservedly famous text-book of pathology which appeared less than twenty years ago, the index includes forty references to viscera attacked by syphilis without any mention of heart or aorta; and that the aortic lesions of syphilis receive, in the whole book, no more than half a page, within a paragraph, on the vascular aspects of the infection. Two lessons, were learnt, however. One was the syphilitic origin of many cases of aortic aneurysm. Welch did not put this above 50 per cent., but recent writers ascribe the majority of thoracic aneurysms to syphilis (Lian 83 per cent., Stewart and Garland 75 per cent.). Then again the writings of Phillips, Wilks, and others, showed that as a cause of sudden death and less disastrous manifestations of myocardial disease syphilis had to be reckoned with. Meanwhile, and in spite of the teaching of Allbutt and Broadbent, the fact that aortitis is a common result of syphilis still remained in the background. We owe its emergence to the morbid anatomists, who insisted with increasing emphasis on the importance of syphilitic aortitis as a cause of death. Now, however, the fact is generally recognized. Oberndorfer (Münich), for example, found this lesion in 7 per cent. of all autopsies; Reid (Boston) in 3 per cent., as also Symmers (New York); Clawson and Bell (Minneapolis) 2.6 per cent; Wittgenstein's figures come out below 2 per cent. Cohn, summarizing American data, thought deaths from cardiac syphilis accounted for 4-6.8 per cent. of all autopsies. In Bristol (Taylor) the figure was 2.5 per cent., and at St. Bartholomew's Hospital (Cullinan) 3.3 per cent. Most of these observers have compared the incidence of aortitis with that of other syphilitic lesions and find that it easily surpasses them all. It is probable, however, that some of the higher statistics overstate the syphilitic element in aortic disease. The writer has elsewhere offered reasons for believing that the naked-eye appearances of aortic disease may suggest a syphilitic basis which is not substantiated by histological inquiry. The margin of this error would doubtless vary with different observers, and this makes it a little difficult to compare one set of observations with another. Here and there, indeed, are to be found data covering periods of some years, and emanating, if not from a single observer, at all events from a single pathological institute. Such are the figures drawn from 70,000 autopsies by Langer, who believes that they prove an increase in the incidence of cardio-aortic lesions in syphilitic subjects from 33 per cent. in 1906 to 84 per cent. in 1925.

On the other hand, clinical evidence supporting a belief in the increased incidence of cardio-aortic syphilis is hard to come by. For example, Kolle and Laubenheimer have shown that in Frankfurt during the years 1910-16, as judged by serum tests, the clinical incidence of aortic syphilis has remained stationary. In this country the deaths from aneurysm show a slight decline, and when allowance has been made for the more accurate

diagnosis of aneurysm rendered possible in recent decades by the X-ray screen and the Wassermann test, it is clear that this, the grossest clinical evidence of aortic syphilis, is decreasing rather than increasing. There are several explanations by which an apparent decrease in the incidence of aneurysm might be made plausibly to accompany a stationary or increasing incidence of syphilitic aortitis. Some unknown factor which, having ceased to operate, has left the whole field to syphilis; an improvement in treatment whereby aortitis has been scotched but not killed; or a redistribution of patients by which the sufferers from aneurysm have been segregated to some institutional limbo where they escape observation; all these fall to the ground for want of evidence, and it remains probable, though not proved, that in this country, at all events, the incidence of cardio-aortic syphilis is not actually increasing.

Even so, however, there are several reasons for respectful consideration of aortic syphilis as a cause of crippling and death. First of all, even after every reasonable reduction has been made, the irreducible total which remains constitutes a large proportion of all serious cardiovascular disease. This varies somewhat in different countries. In Great Britain the percentage appears to be 5-10; in the United States 10-15 per cent. (though in Oregon, Coffen, and in Utah, Viko, found it much lower); in South Africa about 15 per cent. (Heimann in Johannesburg); and in France and middle Europe perhaps even a little higher. Then, again, the outlook after diagnosis is almost desperate. Figures drawn from the writer's own experience showed that the average duration of life, in a group of fatal cases, was two and a half years from the onset of symptoms. Probably the average expectation of life in the whole series was not more than five years. This may be compared with Mitchell Bruce's estimate of five and a half years, and with Deneke's of something over four years; with an Italian average of three years; and with Brockbank's one to four years. Scott, indeed, says he has known aortic leakage begin eighteen years before death, and the writer had under observation one patient who showed signs of the same lesion for ten years before he died. Hubert, on the other hand, put it at eighteen months in hospital and three years in private cases. The average seems to lie round about five years. This fact may be viewed from another standpoint. If it be asked how syphilis kills, the answer, according to Symmers, Langer, and others, is that cardiovascular disease is probably its most lethal result. Symmers's figures, from New York, may be taken as an example. In 4,880 autopsies he found syphilitic lesions in 314 subjects; aortitis and its effects in 175, nervous lesions in 112, hepatic syphilis in 105, and lesions of the respiratory tract in 35. Turnbull, in London, found aortitis in 175 out of 288 autopsies of patients bearing marks of syphilis—a close agreement with Symmers's New York data. These figures show that in these days syphilis is chiefly to be feared because of its action on the aorta and heart.

There is no reason to believe that the aorta is becoming less liable to suffer when exposed to the action of syphilis. Considerations of the

pathology of the disease, to be set forth presently, support the view that if the infection be not checked in its earlier phases, some measure of aortic destruction is inevitable. It follows, therefore, that if the incidence of syphilis increases that of aortitis will increase also, unless the increase of syphilis has synchronized with so great an improvement in therapeutics that it has been neutralized by a corresponding, or even overtopping, percentage of cure. Now, there is little doubt as to the increase in the incidence of syphilitic infection which accompanied and followed the European War. The actual figures are available, we believe, only for the post-war period; so far as these go they are striking, for, as L. W. Harrison interprets them, they prove an inflow to the treatment centres of England and Wales of nearly twice as many cases in 1920 as in 1925.

Now, since it is agreed by all observers that the latent period elapsing between the primary infection and the onset of cardiac symptoms is fifteen to twenty-five years, it follows that we have yet to see whether the increase of primary syphilis noted in, say, 1920 may not bear fruit as an increase of aortic disease in 1935-45. If it does not, the credit will be due to the treatment which, in the intervening years, has been so thorough and successful as to cut the infection short in a majority of the cases to which it has been applied; and those in whose hands the treatment of syphilis lies will be encouraged in methods that can claim so signal a proof of their success. If, on the other hand, an increase in the incidence of cardiac syphilis is experienced, we shall be obliged to admit that our plans of treatment, however carefully conceived and thoroughly executed, have nevertheless been defective or misdirected.

Moreover, the mere prospect of an increase in the number of patients in whom this form of heart disease is to be diagnosed and treated brings home the need for a revision of the methods available for these procedures. Confronted by this task, we hear a faint echo of the arguments by which, at the beginning of this century, it was hoped to prove that the progress of locomotor ataxia and general paresis could be checked by early diagnosis and persistent treatment; and also of the confession of disappointment by which those arguments had to be refuted. Is there anything to be learnt from a comparison of this new problem with that older one? That the two are closely allied is proved, not only by the broad similarity of the clinical facts, but also by the frequent association of circulatory with nervous syndromes in the same person—an association the fullest development of which is seen in the familiar coincidence of tabes and aortic aneurysm. In the writer's series of 103 cases of cardiac syphilis there were also tabo-paralytic signs in sixteen, and focal syphilis of brain and cord in others. This experience is paralleled by that of Hubert who found tabes in 25 per cent. of 300 cases of cardiac syphilis. The same relation has been expressed from the opposite end by Hopkins who noted ninety-eight examples of cardiovascular infection in 1,371 cases of neurosyphilis. In Kimbell's series of fifty-four cases of cerebrospinal syphilis there were eighteen patients who also

exhibited signs of cardio-aortic infection. Guilly in 200 cases of general paralysis, examined *post mortem*, found evidence of aortic disease forty-one times.

One may perhaps claim another parallelism in the fact that both organs, the heart and the brain, while chiefly liable to these diffuse and progressive lesions of structure and degradations of function, are also from time to time the seat of focal lesions. In some instances, indeed, the same heart may, as the same brain may, exhibit within its bounds these two separate and independent consequences, the gumma and the diffuse degeneration, resulting from the same cause though in a different way, each working out its own destiny. Indeed, it is perhaps not pushing the analogy too far to claim that, as in the neuraxis, so also in the heart, two kinds of focal lesion may be discerned. Corresponding to the meningovascular damage resulting in strokes if in the brain and paraplegia if in the cord there are cases of subacute myocarditis occurring early in the career of the syphilitic, such as are noted by Gravier, Carter and Baker, and others. These cases are notably rapid in their onset, and they react to treatment even more favourably than do the gummata; although the two groups together unfortunately constitute only a small percentage of the cases of cardiac syphilis seen nowadays. Even earlier still—before the rash comes out—what Gravier calls coronaritis has been observed by several pathologists. Taylor of Bristol is at present at work on a possible example of this lesion from a patient under the writer's care. There is, then, what may be called a series of focal lesions to be discerned in the injuries which syphilis is capable of inflicting on the heart; an acute vascular inflammation in the early secondary stage, a subacute myocarditis arising as a rule several years later, and gummatus infiltrations encountered later still. In fact, the similarity between the two sets of changes, the vascular and the nervous, is so close as to lead irresistibly to a fresh scrutiny of their origins.

The Essential Lesions of Cardiovascular Syphilis

If the cardiovascular lesions be inspected from the point of finding what are the predominant changes, there can be no doubt that aortitis is the most constant. For example, in Turnbull's series aortitis was found four times as often as scarring of the aortic cusps, and far oftener than gross myocardial disease. The same kind of experience is recorded by Saphir and Scott, and also by Martland and by Carr. Allowance must be made for the fact that there is an 'essential' ventricular hypertrophy in cardiac syphilis, as Gallavardin and Carr note; and also for the fact that close scrutiny of the commissures of the aortic valves will reveal early changes in many instances where the cusps themselves are uninjured. But after all this has been conceded, it still remains true that the predominant lesion of cardiac syphilis is aortitis.

If this search be pursued a stage further, the peri-aortic origins of the lesion will be recognized. The cellular infiltration that is its distinctive

mark wells out of the mediastinal lymphatics in the direction of the aorta and is piled up on the outer surface of the adventitia, especially on that part of it which clothes the first two or three inches of the ascending aorta. Thence it seeps through the media by following into it the vessels which pass in thither from the adventitia. These vasa vasorum, surrounded by, and one might almost say soaked in, the peri-aortic fluids, swell up almost to the point of extinguishing their channels. The cells which accompany them into the media tend to pass between contiguous laminae of elastic tissue, separating these from each other. Then, as the cell-distended spaces increase in size, one breaks through a lamina into the next space, and perhaps through yet another lamina; so that at length a formidable breach has been made in the elastic wall of the aorta. Although this may be to a small extent neutralized by thickening of the intima at the point where the media beneath it is weakened, the general result is to create a weak spot at which the pressure within the aorta can force outwards the damaged remains of the wall into an aneurysmal bulge. Even if the breaches of continuity are not as gross as this, their effect on the work of the heart must be very great, since they depreciate one of the chief forces by which the ventricular force is economized, namely, the elasticity of the aortic wall.

But perhaps the most deadly blow which syphilis strikes at the heart is that which is less obvious than either of these. In a quarter of the specimens examined by Scott, and in 15 per cent. of Martland's, the orifices of the coronary arteries were more or less tightly strictured. This is due to the spread of the infiltrative process from above to the sinuses of Valsalva. Here it stops; at all events it is not to be found in that part of the cardiac wall which lies immediately below the coronary openings, nor does it spread along the coronary arteries themselves. These, indeed, are remarkably free from syphilitic disease of any kind, and the cellular infiltration that has been traced to the angle which the wall of the coronary artery makes with that of the aorta, leaves off at that point with conspicuous abruptness. The coronary trunks and branches naturally exhibit atheromatous change in a number of instances, since the disease is one that occurs at the atheromatous age; but this relationship is coincidental and not causal. Even apart from any concomitant atheroma, however, the injury inflicted on the wall of the heart by stricture of the coronary mouths is very severe. Areas of muscle are starved to such a degree that, as Wearn showed, the Thebesian veins are actually requisitioned to bring blood to the hungry muscle from the ventricular cavity direct. Small wonder that patches of the cardiac wall become atrophic and display as gross a replacement fibrosis as is seen anywhere in the body. These myocardial changes include a watery state of the heart-muscle which some authorities have interpreted as a feeble inflammatory reaction excited by residua of spirochaetes. It is, however, so improbable that an irritant as intense as the spirochaete has proved itself to be at the stage of inoculation could excite so feeble a reaction, that if this were the only hypothesis accounting for the myocardial lesions

it could only be accepted provisionally in the hope that something more plausible would manifest itself. Fortunately, however, there is no need to wait for an alternative. The relation between coronary stricture and myocardial fibrosis is, after all, traceable in several kinds of coronary disease, and finds its plainest expression in the case of syphilis.

The result of the arrest of their heartward flow is that the cells are found to be aggregated in the commissures from which the semilunar cusps of the aortic valves spring, spreading thence, heralded by oedema, into the cusps themselves. These are stiffened and also tethered at the commissural ends; loss of endothelium may be followed by adhesion of cusp to aortic intima, or of cusp to cusp; the oedematous cusp may perforate; and in one or more of these several ways the aortic cusps are so injured that they fail in their function, and aortic regurgitation ensues. In passing, it must be noted that on this basis of valvular injury a streptococcal infection may be superimposed, and a progressive endocarditis, acute or chronic, thus initiated.

Now, the main purpose of this brief review of the histological pattern of cardio-aortic syphilis has been to bring into prominence two facts; that the whole process is set in train by something which is brought to the heart from without by lymphatic channels, and that the heart is scarcely so much invaded as blockaded—compelled to surrender by reduction of its supplies.

As long ago as 1918 Klotz, in a paper which was overlooked by most writers but not by Clifford Allbutt, said that in his investigation of a series of autopsies on persons with syphilitic aortitis he had been able 'to demonstrate a chronic mediastinitis which . . . had a distinct course along lymph channels to and from the mediastinal lymph glands'. Along these tracks he found occasional spots of more active reaction; but actual gummates in only one instance. The glands themselves showed but little change. Klotz pointed out that the peri-aortic lymphatics are most numerous on those parts of the aorta that come into near relation with lymph glands, and therefore on the thoracic arch.

What is true of cardiac syphilis is also to some extent true of cerebro-spinal syphilis. Each group of lesions is divisible into diffuse degenerations which are the rule and focal inflammations which are the exception. Those lesions which are the rule display in each case two principal features; within, an atrophy of degeneration of special parts and tissues; without, a cellular infiltration, mononuclear in type, finding contact with the diseased organ through the medium of external lymph channels. Stern, who has recently published an account of researches into the histopathology of tabes dorsalis, suggests that the toxins responsible for the degenerative changes in the posterior columns must come from some reservoir of infection not far removed from the dorsal cord, and suggests that it may be the aorta that is that reservoir. This hypothesis, attractive though it is, does not explain the simultaneity of the aortic with the tabetic lesions; indeed, the cord symptoms are on the average earlier in the course of late syphilis than those of the aortic lesions. It has already been suggested that

both cord and aorta may derive their lesions from some common source, such as the lymph glands within the thorax. The additional evidence that can be called to support this view is indirect but coherent, as the following observations may show.

In the first place, the last overt act of the spirochaete in the ordinary case of syphilis is the provocation of a lymphadenitis. If the old clinical nomenclature be revised in the light of the new knowledge, then the primary lesion might be named the stage of inoculation, the secondary stage that of bacteraemia, and the tertiary stage that of residual granulomata. The bacteraemia of the secondary stage has—save for the occasional granuloma, excited by residual spirochaetes—been brought to an end by a general lymphadenitis. It is to be presumed that in this the lymph glands have exercised to the full their function as traps for bacteria, and that if they have successfully performed their functions the other tissues have been cleared of spirochaetes.

The second point that appears worthy of consideration is the part that the lymph glands play in the course of experimental syphilis. Many workers, among whom Brown and Pearce should be particularly mentioned, testify to the fact that the virus lives on for long periods of months, and even years, in the lymph glands of animals that have been experimentally inoculated with the *Spirochaeta pallida*; and that when it is necessary to transmit the infection to another animal this can be done by using emulsions of the lymph glands from the first animal for inoculating the virus into the second. This 'carrier' function is not limited to those superficial glands which have been infected by direct spread of the spirochaetes from the point at which the skin was transgressed by the primary lesion. It holds good also for deeper and more distant glands, for example, those within the abdomen. L. W. Harrison says that 'general adenopathy is probably the most persistent macroscopic feature of syphilis' in man; and that 'lymph glands are the principal harbourers of virus in latent syphilis'.

Third, Levaditi, Schoen, and Sanchis-Bayarri say that the glands of infected rabbits contain granular material that takes the stains commonly used for spirochaetes. This they regard as representative of some non-spirochaetal phase of a life cycle through which the organism that we know as the spirochaete is passing. Similar observations by Saleeby and Greenbaum are interpreted a little differently, for they look upon these argyrophile fragments as being indeed spirochaetal, but degenerate and breaking-up. Levaditi and his co-workers note that these glands can be used to transmit the infection to other rabbits. From some investigations it seems that the same infectivity may actually be claimed for the deeper lymph glands from human beings with general paralysis, at all events in a proportion of cases. Fischer, for example, states that although he himself failed in eight cases of general paresis to prove that the lymph glands were infective, Engmann and Eberson succeeded in three out of fourteen cases.

If each of these steps should be substantiated the result would be an

argument in favour of belief in a lymphogenous stage of the spirochaetal process; a stage characterized by the issue of virus—whether particulate or humoral, or both, yet in any case spirochaetal—from the lymphatic reservoirs in which it had been stored; an overflow thence into lymphatic channels and thus into such organs and tissues as happen to be in the way.

There are, it must be admitted, many gaps in this argument; but it is at least as plausible as that which attributed the whole of the aortic and cardiac troubles to a blood-borne infection, and claimed that this laid down deposits of spirochaetes here, there, and everywhere. To this view, urged so persuasively by the late A. S. Warthin, there are obvious objections. One is that many skilled observers, among them Turnbull, Clawson and Bell, and Saphir and Scott, have failed to find spirochaetes in the aortic lesions. Even more difficult is it to understand how an organism which is injurious enough to excite so violent a reaction as that of the primary sore, and so toxic an illness as that of the secondary stage, could settle down in the cardiac wall and provoke no local response other than the outpouring, in moderate quantities, of plasma with nothing in it except an occasional plasma cell. It is not to be wondered at that even when these views were first promulgated, they did not command general assent. Now that there has been time to consider their applicability to the clinical facts and also to test some of the evidence on which they were based, there is—even in America, where their author's prestige commanded for them a natural respect—a reaction against that view, as the papers of Martland, and Saphir and Scott, show. Martland, in supporting the lymphogenous view propounded by Klotz, adds to it the interesting suggestion that, since it is probably from the lungs that a large proportion of the spirochaetes are collected into lymphatics at the end of the secondary stage, it is also probable that the lymph glands of the mediastinum receive more than their share of the spirochaetes which are committed to them for disposal; and that this accounts for the heavy incidence of these later changes on the aorta and dorsal cord. The fact that Warthin and others have demonstrated large numbers of spirochaetes in the wall of the heart, with local reactions, both in congenital and in early acquired syphilis, does not disturb the lymphogenous view; for at that period of the infection all the tissues are more or less saturated with spirochaetes.

The main fact, that of the capacity of syphilis to lie latent and at the end of one or two decades of latency to kill, is not in dispute. And when it does emerge from its subterranean bed into daylight, the course of the disease has divided into two main streams. There are others, but the two chief ones, flowing in parallel courses and mingling from time to time, are the cardio-aortic and the cerebrospinal. Whatever view may be held of the nature of the latent period, there can be no doubt about the close relation between these two sets of phenomena. As we have seen, there are histological similarities; they often coincide in the same individual; it is at about the same period, fifteen to twenty-five years after the primary

inoculation, that each is likely to occur ; in each there is the same insidious onset, and yet a strong probability of ingravescence once the symptoms have appeared. This close parallelism with taboparalysis does not encourage an expectation of therapeutic triumphs, yet it emphasizes the need for early diagnosis, since it is only by this means that a stage susceptible to treatment can be brought to light.

Diagnosis

What is 'early diagnosis' of syphilitic aortitis? How soon after the aortic tissues have begun to suffer anatomically do they make a complaint which is audible clinically? As has already been shown, it is difficult to assess precisely the interval that elapses between the entrance into the body of the initial dose of infection, and the beginning of an aortitis. The available evidence seems to suggest that this period of incubation does not necessarily exceed a year, and this agrees well enough with what might be expected if the lymphogenous theory is correct. For on that hypothesis, the spirochaetes that have, after three or four weeks' incubation in the primary sore, burst through the local barriers into the blood-stream and thus gained access to the whole body, find themselves swept up into the lymph glands within another couple of months ; so that within three months from the primary inoculation a reservoir of spirochaetes has been formed, from which—if the 'tempo' of the movement may be measured by the type of cell that predominates in the inflammatory reaction of the peri-aortic tissues—something injurious to those tissues has emerged within a further period to be estimated in months rather than years.

On some such hypothesis as this it is easier in syphilis to understand the long latent period that separates the overt act of inoculation from the earliest signs of its visceral lesions than it is in some other infections. For example, how is the gulf bridged that separates the tonsillitis of childhood from the advanced nephritis of early maturity? All sorts of explanations may be advanced, but none of them is based on a solid groundwork of evidence. Here, in the case of syphilis, there is at least a hint of evidence in the shape of the signs of attack on the aortic wall delivered along the lymphatic paths. And that attack, it may be supposed, does not cease so long as there are living spirochaetes within the body.

This, then, is the first fact to be remembered when the diagnosis of aortic syphilis is being considered ; that in all probability the aorta of every person infected with syphilis has suffered a certain amount of damage within a year or so of infection. That is the kind of reflection which should encourage prolonged and thorough treatment of every case of syphilis ; and it is powerfully reinforced by the conviction that naturally arises from it, to the effect that so long as the syphilitic virus is alive within the body, the aortic lesions are in danger of progressive aggravation. One might almost go so far as to say that every case of syphilis is a case of syphilitic

aortitis, were it not a matter of common experience that many persons who have without doubt been infected have nevertheless reached maturity and even lived a normal term of years without developing any clinical evidence of aortitis. This view is remarkably supported by the series collected and analysed by Brunsgaard, whose cases were those of persons whose infection escaped specific treatment in those earlier stages when such treatment is effective, if ever. His figures were based on a study of 309 patients, among whom signs of cardiovascular disease, though commoner by far than in any other organs, were discovered in 14 per cent. only. Saethre's statistics are very like these. Among 371 patients, living or dead, investigated ten to forty years after infection, 65, or 17.5 per cent., exhibited signs of aortitis and other vascular lesions. These figures also agreed with those of Brunsgaard in that both series proved aortitis to be much more likely to occur than taboparalysis—ten times more likely in Saethre's series; which, it should be added, was also limited to persons who had had no specific treatment. These series show that aortic disease is not an inevitable result of syphilitic infection, even if inadequately treated.

But even if these figures prove that it is far from the truth to claim that aortic lesions develop in a majority of cases of unchecked syphilis, yet they do at least show that if the infection makes any impression that is clinically appreciable it is more likely to be on the aorta than on any other structure. There is, therefore, some justification for the belief that various investigators have entertained—in the possibility of an early diagnosis of visceral syphilis by means of careful attention to the cardiac physical signs. For example, twenty years ago Breitmann, addressing himself to this same task of finding evidences of cardiac disease in secondary syphilis (necessarily without the help of electrocardiography), said that in many cases there were disturbances of rhythm, as well as dyspnoea, dilatation murmurs, and aortic incompetence, often transient. Grassmann also made a similar claim. On the other hand, Follows, of Liverpool, in a research, the drift of which he kindly communicated to the writer before it was quite complete, found only slight alterations of the electrocardiogram in fifteen out of sixty-eight cases of early syphilis investigated, the remainder being normal. Cassidy in twelve early cases of syphilis, also related to the writer in a personal communication, found eight normal and four showing trivial changes. Turner and White, in fifty early cases, found no gross abnormality, and Arnett's experience also agreed with this.

Similarly, several physicians have examined series of children with congenital syphilis. Previtali, Nicholson and Moor-Adams, using all methods, including X-rays and electrocardiography, were unable to find any evidence of aortic disease in fifty congenital syphilitics; Givan was as unsuccessful in an even larger series of 417; and so was McCulloch who followed his patients to the age of 15. Yet it is improbable that among all these children there was not a single one who would later on display evidences of aortitis. Kuntz and Eyster, indeed, and also Beretervide, think that

radiography can discover early aortic increase in syphilis. It does not, however, appear that either of these series was followed long enough to trace the course of the aortic lesions thus discovered, or thought to be discovered, in an early stage. The claim that aortitis due to congenital syphilis can be diagnosed by radiography long before it is perceptible in any other way seems to fall under the warning uttered by Conner and Thayer, against diagnoses of aortic syphilis based on the unsupported testimony of the X-rays. The truth seems to be that however carefully the course of syphilis may be watched, neither symptoms nor signs of aortic disease are recognizable until a period of fifteen years after primary infection at least has passed. There are exceptions to this rule such as those recorded by Osler, Liek, and others. In Leschke's series the shortest latent period was six years, but even when this was included, the average period elapsing between primary infection and onset of aortic symptoms was twenty-two years; in Turnbull's series the same figures were eight and twenty-five years respectively; in that of Carter and Baker, three and fifteen and a half years.

If, therefore, we must regretfully admit our inability to detect early phases of an aortitis which, in some instances at least, is none the less surely developing, it is all the more incumbent on us to recognize two plain necessities; that of thorough and prolonged treatment in every case of syphilis, and that of studying carefully the symptoms and signs by which the existence of an aortitis may declare itself. Even if this cannot be called early diagnosis, it is at least the earliest that can be made.

Now, if symptoms as a whole be compared with signs as a whole, it will be found that in most cases of aortic syphilis symptoms appear before signs. The commonest early symptom in the experience of the writer has been dyspnoea. Some observers (Keefer and Resnik) consider that paroxysmal dyspnoea occurring at night is peculiarly common in aortic syphilis. It would, perhaps, be more in accord with general experience to say that dyspnoea of this kind is usually associated with the ventricular defeat of chronic hyperpiesis; and that in aortic syphilis the dyspnoea is not usually different from other forms of heart disease.

There is, however, a general agreement as to the peculiarities of the praecordial pain experienced by the cardiosyphilitic. Willius and Barnes, for example, noted anginal pain in 50 of 140 patients with aortic syphilis; but in only six of these was the pain typical. Figures published by Carter and Baker appear to support the view expressed elsewhere by the writer, that in such patients the pain is apt to occur spontaneously, for instance, during rest in bed, differing then from the 'ischaemia cordis' of the angina of effort. Stolkind notes the same fact and relates illustrative cases. There is also reason for thinking that its distribution is less characteristically central; that it is more apt to be referred to the shoulders, the back of the neck, and other relatively remote regions, than the pain of coronary atheroma. The writer encountered one striking example of pain on swallowing as the first symptom of aortic syphilis. Not even at autopsy,

however, was it clear how the aortic lesion that was found could have caused this.

To the broad rule that symptoms precede signs there are two exceptions. The first group comprises those patients who die suddenly without ever having experienced any symptoms that they deemed worthy of complaint. These people are so seldom examined that it is not possible to say whether in most of them physical signs would have been found before the fatal attack. Occasionally, however, such patients are known to have had aortic incompetence without dyspnoea, pain, or other subjective discomfort. Then, again, there is the group of patients who come under observation because of some other syphilitic lesion and are found in the course of a general examination to present evidence of aortic disease. It is from this group rather than the other that we are likely to learn lessons in diagnosis; for in such patients we may be able to detect evidences of dilatation of the aorta before the valves have become incompetent. This is what we ought to attempt, as MacLachlan argues; for when the aortic valves have begun to leak, the chances of doing much good by treatment are small. Hines and Carr's figures support this; they show that symptoms were tangibly relieved by treatment in almost three-quarters of their cases of uncomplicated aortitis, but in less than half of those who had developed aneurysm or aortic regurgitation. The reasons for this contrast are simple. Not only does aortic leakage add greatly to the burden of the left ventricle, already embarrassed by a perishing aorta; but also it implies that the infiltrative process is at the base of the aorta and threatening the coronary mouths. Hence the need of diagnosis before leakage has begun. How is this to be accomplished?

The aortic lesion is divisible into three phases; that of the aorta itself which becomes stretched; that in which the aortic valves are rendered inadequate; and that which is characterized by coronary stenosis. If, therefore, aortitis is to be detected before it has led to valvular or coronary lesions, it can only be by virtue of the aortic dilatation which it causes. The physical signs which justify a diagnosis of dilated aorta are well known and scarcely need more than a word. Careful percussion both down and across the manubrium; detection of the emphatic second sound, the 'bruit de tabourka' of Potain, especially in the presence of a normal or low blood-pressure; sphygmomanometric and other evidences of asymmetrical blood-supply to the upper limbs; all these are well known and reasonably definite. But by the time these signs are recognizable the lesion is already advanced. Can its results be detected earlier by the use of *skiagraphy*? It is very difficult to get to this question a reply which is both unbiased and also informed. Vaquez and Bordet, who have studied the great vessels at the base of the heart by means of X-rays, perhaps as long and as carefully as any one, are accustomed to base a diagnosis of aortitis on widening of the aortic shadow, increase in its opacity, and decrease in its pulsatile excursion. Steinfeld, Pfahler, and Klauder in 105 cases of syphilis found

physical signs twelve times; and X-ray signs of aortitis in nineteen of sixty-three cases examined by this means. Steel says that aortic syphilis may be suspected when the aorta is diffusely dilated without a corresponding enlargement of the heart (an opinion which Parkinson is inclined to endorse); also when a dense aortic shadow, rising high in the chest, is found in a relatively young subject without a high blood-pressure. He goes further, and claims that a diagnosis of aortic syphilis can be made with confidence, when the aorta shows a localized dilatation with a local increase of pulsation. Groedel details radiographic appearances by which he can discriminate between aortic syphilis and arteriosclerosis. Kuntz and Eyster, limiting their X-ray studies of the aorta to persons known to be syphilitic, found that of forty males with acquired syphilis only two showed no X-ray signs of aortitis; while among fourteen female patients three were negative. The same writers found one boy out of four and five girls out of eight with congenital syphilis, free from these signs; which they also noted in twenty-two out of twenty-three cases of neurosyphilis. Their criteria are elastic since they include within the signs of aortitis any demonstrable change—elongation or tortuosity, widening of any portion, pulsation to the right of the sternum, increased density leading to visualization of the descending aorta. Erdeyey goes so far as to claim that it is possible to judge, from the degree to which the shape of the transverse aortic shadow is altered when the patient swallows, whether the walls of the aorta are sclerosed or not. Bordet also says that aortitis can be detected by skiagraphy several months before clinical symptoms appear, largely by noting variations in the opacity of the aortic shadow. Hampton, Bland, and Sprague also carry this claim to the validity of purely radiological diagnosis to an extreme; they describe a careful technique for measuring the aorta which seeks to establish an absolute standard of aortic diameters, the surpassing of which they regard as proof of aortitis. In discussing these claims Conner and Thayer deprecated the attempt to base diagnoses of aortitis on skiagraphy alone. The variations within the normal are too wide to justify attempts to draw a hard and fast line between what is natural and what is morbid; and this general principle of diagnosis, which has already been applied to every stage in the evolution of modern medicine, is applicable once again here. At the same time there is not the least doubt that skiagraphy can often clinch a diagnosis of aortic syphilis when nothing else can, by proving that the aorta is enlarged in circumstances justifying a belief that the enlargement may be caused by syphilis. That is as near as it seems possible to get, in the present state of knowledge, to an 'early' diagnosis of aortic syphilis.

There remains, however, the less ambitious task of recognizing the syphilitic basis of established cardiovascular disease. There is a real need for this, not only because of the help that it gives to treatment, but also because it is essential to accurate prognosis. It is therefore worth while to spend a short time in a review of the grounds on which a cardiovascular lesion may be regarded as syphilitic.

First of all, then, the anatomical pattern of the lesions is of importance. This at all events will probably be, in a majority of instances, the first thing that will suggest to the clinical observer the syphilitic aetiology of the troubles under consideration in a given case. The commonest clinical pattern is that of aortic incompetence. This was present in 61 of the writer's 103 cases of cardio-aortic syphilis, in 59 per cent. of those reviewed by Willius, and in just under 50 per cent. in Heimann's and Reid's series. Conversely, Harmer found that of his series of cases of aortic incompetence in persons aged from 20 to 70 years 37 per cent. were syphilitic. Cowan and Faulds noted a syphilitic basis in 32 per cent. of their series of persons with aortic valvular disease. Leschke puts it at something over 60 per cent. and Wittgenstein at 75 per cent.

Aortic stenosis, on the other hand, is not often syphilitic; Christian, describing a group of cases under his observation, got a positive reaction to the Wassermann test only twice in twenty-one endeavours. The reason for this is obvious; the syphilitic process attacks the cusps from their commissural attachments and renders them grossly incompetent before any secondary process of valvular sclerosis can develop to the point of obstructing the aortic channel. Gallavardin and Gravier, it is true, describe a syphilitic valvulitis leading to stenosis, but they admit that it is very rare.

Aneurysm of the thoracic aorta has become a relatively rare disease, but when it occurs it is almost as accurate to assume it to be syphilitic as it is of tabs. In Major's series the Wassermann reaction was positive in 95 per cent.

There is also a not inconsiderable group of cases with little in the way of physical signs, but serious symptoms; it is difficult to define these precisely, but it may be said that any man of middle age who displays signs of myocardial disease without obvious cause should be suspected of syphilis.

On the other hand, there are forms of cardiac disease which are not often syphilitic. For example, it is difficult to see how mitral stenosis could ever be caused by syphilis. The morbid process that ends in mitral stenosis is essentially blood-borne, while the syphilitic approach to the heart is, as we have seen, essentially lymphatic. Several writers, chiefly in France, have supposed that congenital mitral stenosis might be an exception to this rule, but since the pathological process of congenital syphilis is not different from that of the acquired infection, it can hardly be thought capable of different end-results.

There are other forms of cardiovascular disease, however, where a syphilitic element might more logically be suspected. Indeed, it was long thought that chronic focal myocarditis of the kind that finds its plainest clinical expression in heart-block, was more often syphilitic than not. However, recent experiences have shown that syphilis is only responsible for a small percentage of cases of complete heart-block (10 per cent. or less—Gallavardin, Herapath). In Campbell and Turkington's series of fifty-six cases of bundle-branch block syphilis was only thrice responsible. The reason

for this is perhaps to be found in the diffuse distribution of the myocardial changes in syphilitic heart disease, which in its turn is due to the fact that these changes are almost wholly caused by coronary stenosis and consequent myocardial ischaemia; scarcely at all to direct infection of the myocardium by the spirochaete.

It is true that in senile cardiosclerosis, which is the usual background of heart-block, the foci of degeneration in the myocardium are, as in syphilis, the outcome of slow starvation due to coronary disease; but whereas this is a leading feature of the decrescent process, it is in syphilis secondary to serious degeneration of the aorta, and therefore liable not to develop till it is either overshadowed or anticipated by other phenomena which are speedily lethal.

Another clinical pattern of cardiovascular disease in which one might at first expect to discern the influence of syphilis is that of cardiac infarction. As a matter of experience, however, this is not so (Levine, White and Bland, Coombs). This, again, accords with the anatomical facts; syphilis narrows the coronary orifices but scarcely ever attacks the vessels in their course. Some interesting exceptions have been recorded, among them several instances in which a coincidence of coronary obstruction with pancreatic glycosuria has appeared to be referable to a syphilitic basis. Perhaps, however, a similar coincidence would prove even more frequent if a series of cases of progressive arteriosclerosis were reviewed from this standpoint. The orificial stenosis of the coronary arteries that is so characteristic of the cardiosyphilitic anatomy has its characteristic counterparts on the physiological side. We have already noted the fact that praecordial pain is often experienced by these patients. In the writer's tables pain which appeared on clinical grounds to be cardiac, and in most instances ischaemic, was felt by 43.2 per cent. of the cardiosyphilitic patients and by 29.2 per cent. of those with senile cardiovascular degeneration. The fact that there is also in the syphilitic patient a liability to pain even during rest, and to pain of an unusual distribution, may perhaps be interpreted as evidence that there is in the syphilitic patient a peri-aortic origin for the pain as well as a myocardial, whereas in the cardiosclerotic subject the pain is myocardial only. But even if we carry this hypothesis as far as it will go, there remains the fact that in many cases of cardio-aortic syphilis the pain is both in its distribution and in its relation to effort, closely similar to that experienced by persons with cardiosclerosis. Probably analysis of the facts would show another small difference in respect of prognosis; the average expectation of life would probably turn out to be shorter in anginous subjects with a syphilitic lesion than in those who are merely cardiosclerotic. The figures recently published by White and Bland support this view.

A second feature of the clinical pattern woven by the cardio-aortic lesions of syphilis is the type of myocardial failure that it causes. We have already seen that localized changes, such as those which lie at the back of the various kinds and degrees of heart-block, are rarely caused by syphilis. It

is, therefore, no surprise to discover that auricular failure—usually the outcome of changes which, if not actually localized to the auricular walls, nevertheless attack them with peculiar intensity—is a rare mode of cardiac defeat by the syphilitic process. Herapath and the writer found that in less than 2 per cent. of a series of cases of auricular fibrillation could syphilis be held responsible, and also that in a series of 103 cases of cardio-aortic syphilis auricular fibrillation was only observed eight times. This corresponds on the one hand with the data collected by Vela whose series of 105 cardiosyphilitics examined by electrocardiogram included only six examples of fibrillation; and on the other hand with those of Campbell, who found syphilis responsible in only two out of 100 cases of auricular fibrillation. In the experience of Carter and Baker the syphilitics accounted for 3 per cent. of the fibrillation cases.

In contrast to this Parkinson and Clark-Kennedy noted a syphilitic basis in 21 per cent. of their patients exhibiting the syndrome which they describe as heart failure with normal rhythm; and in the writer's series of 103 cases of cardio-aortic syphilis evidence of enlargement of the left ventricle was noted in 80, while signs of gross ventricular failure were conspicuous in 20. It is the left ventricle that is singled out because, in the first place, myocardial changes that are generally diffused through the cardiac wall are apt to express themselves most clearly in so far as they undermine the efficiency of the ventricular mass, and particularly that of the left ventricle; and also because it is on the left ventricle that the burden imposed by an aorta which has lost its elasticity, with valves which have lost their efficiency, falls most directly.

Then, again, the syphilitic type of heart disease is notoriously liable to end in sudden death. It is possible that the importance of this association has been exaggerated. The number of sudden deaths attributable to coronary thrombosis—which, as was shown above, is not often caused by syphilis—is perhaps greater than was suspected until recent years, and indeed the apparent increase in its incidence is a phenomenon sufficiently disquieting to call for a closer scrutiny than it has yet undergone. With our facts in so unsettled a state it seems impossible to express in statistical form the liability of the cardiosyphilitic to sudden death, or the probability that behind such catastrophes a syphilitic process may be discovered. Martland, however, discloses the significant fact that in 101 out of 300 cases of sudden cardiac death in which he made autopsies, syphilis was the cause.

Secondly, in the person who has a cardiac lesion of an appropriate clinical type a history of syphilitic infection should be sought. This is not entirely valueless, but there are many fallacies. The patient may give a misleading history, either deliberately or unwittingly. Women are of course particularly liable to make an honest mistake, but men may do the same, as the cases related by Renault show, in which an unmistakable syphilitic infection occurred without any demonstrable primary lesion. On the other hand, even when a history of infection is forthcoming, it does not follow as a

matter of course that any and every cardiac lesion displayed by the patient is syphilitic. It becomes necessary, therefore, to consider further means of ascertaining whether infection is still active.

The most obvious of these is the search for evidence of some other syphilitic lesion. That these are often forthcoming has already been shown so far as the central nervous system is concerned. The extent to which this kind of evidence may be expected to lend its aid is shown by the data of Lennmalm and others. Recently Korbsch has claimed that among these coincidences that of moderate enlargement of the spleen with dilatation of the aorta proves the latter to be syphilitic. Hubert found the spleen clinically enlarged in 26 per cent. of his cardiosyphilitic patients. That visceral syphilis often implicates the spleen is generally admitted, but the experience of most observers would, we believe, be that it is a rare form of the disease as compared with the lesions of the central nervous system. It is perhaps surprising that these latter coincidences do not happen more often, though probably many would claim this fact in support of the view that there are specially neurotropic strains of the spirochaete. At all events it is obvious that the diagnostic value of these facts lies in one direction alone; that is to say, that when signs of syphilitic disease in other organs are found, these are of the greatest value in helping to prove that any cardiovascular lesion present is due to the same cause.

In earlier periods of the syphilitic process there arise opportunities of testing the diagnosis by observing the reaction to treatment. This is a familiar fact and need not be laboured. Here it is mentioned only to confess that in respect of the cardiovascular lesions this therapeutic test is almost as valueless as in taboparalysis. Every now and again a reaction to treatment is surprisingly good; as, for example, in the case of a man whose first admission to hospital was for a frankly syphilitic lesion of the aorta, while at his second visit the signs of this were overcast by symptoms of a superimposed streptococcal endocarditis. Under treatment by novarsenobenzol he made a good recovery from the fever and other evidences of acute infection, and was indeed able to leave the hospital. Again, the writer recalls more than one example of acute and even fatal exacerbation of symptoms on the cessation of potassium iodide administration. But in general it must be confessed that there is little clear proof of a reaction to treatment good enough to be of any diagnostic value.

There remains, then, the Wassermann test. This has been deliberately left till the last because that is the order in which these tests are usually applied. First of all the patient is examined and some view of the nature of his lesions is taken; either these are, or are not, compatible with a diagnosis of syphilis. Then a history of syphilis is asked for; not before, for there are obvious difficulties about making these inquiries a part of one's routine examination. In the meantime, examination of the other organs, and particularly of the central nervous system, may have given some hint of syphilitic disease. If not, and the suspicion of syphilis is

nevertheless strong, it is possible, though not likely, that the diagnosis may be satisfactorily tested by the reaction to treatment. Much more probably it is at this juncture, if not before, that the Wassermann test will be applied. Before discussing the place that this should take in the diagnosis of cardiac syphilis, it will be well to narrow the area to be examined by taking for granted the argument that once the case has been proved syphilitic, whether by serum tests or otherwise, there is not much to be gained from repeating the test. It may of course serve as some guide to the intensity with which treatment must be prosecuted; but it must never be argued that, because a reaction once positive has become negative, the lesion is therefore cured. To make a diagnosis of cardio-aortic syphilis is to discover something which cannot be cured, though perhaps it may be retarded. This may seem an extreme view. The writer has indeed examined more than one aorta in which such lesions as remained to prove that a syphilitic invasion had occurred, were apparently obsolete, or had at all events merged their evil effects with those of a superimposed atheroma. Yet this is so unlikely to happen that it is safer to treat every one with aortic syphilis as 'active' even if all evidences of activity are wanting. It is also reasonable to assume that the accuracy of the test does not differ greatly whether the patient has demonstrable aortic lesions or not. There is no evidence, so far as we know, to show that the syphilitic subject whose aorta is badly damaged is either more or less likely to show a positive reaction to the serum tests than is a patient whose aorta is apparently intact.

If these two assumptions be granted the question at issue is narrowed to a consideration of the value of the Wassermann test in determining whether a person exhibiting signs of cardiac disease, of a not inappropriate pattern, but without other proof of infection, owes that disease to syphilis, or not. The view usually held is that a positive result may be accepted as proof of syphilitic infection. (Goynaroff suggests that simple atheroma may yield a positive reaction, but the two processes so often coincide in the same person that it is impossible to accept this statement.) What is not so certain is the value to be ascribed to a negative reaction. On this there is probably no weightier verdict than that recently pronounced by the Laboratory Committee of the League of Nations. This finding is the outcome of work which has been in progress for some years. It was brought to a head at a Congress held in Copenhagen in 1928 and reconsidered at another meeting in the same city in 1930. The report issued after this meeting, as summarized by Harrison, recommends 'that each serum should be tested by at least two methods, the Bordet-Wassermann and a good flocculation'; and 'that the result should be reported on a uniform plan'. As an example of the reasons underlying the first of these recommendations Harrison quotes a batch of results in which a highly sensitive form of the Wassermann complement fixation method is compared with two flocculation methods.

Method.	Positive Reactions.	
	In 496 Cases of Syphilis.	In 429 Non-syphilitic Cases.
Wassermann	208	0
Muller's 'Ballungsreaktion'	314	1
Kahn's	303	0

The Wassermann technique employed in this series was that known as No. 1 method, Medical Research Council. In Harrison's words, 'any more sensitive Wassermann than this affords false positives'. It is perhaps surprising to learn that even so delicate a technique as this produces results far less sensitive than those of the flocculation tests; and the inevitable deduction is that the average Wassermann test is not seldom negative even in cases where it should be positive. Against this, however, must be considered the fact that in the matter under discussion it is a relatively simple question that the test is required to settle. A lesion of the aorta and heart has already been discovered by clinical means, and it is therefore not a question of bringing to light some early or quiescent focus of infection. The disease, if syphilitic at all, is the outcome of years of infection; and it is therefore likely that the Wassermann test will prove equal to the task of discriminating between these lesions, and those others which produce clinical phenomena simulating those of aortic syphilis. At the same time it is reasonable to hold that if in all its other aspects the case conforms to this diagnosis, a negative reply from the Wassermann reaction should not deprive the patient of his chance of antisymphilitic treatment. Stolkind, for example, relates several cases in which a repeatedly negative Wassermann test was proved by autopsy to have been inaccurate; the patient had well-marked aortic syphilis. Levine (referred to below) gives similar examples.

But should the test be applied more widely still? For example, should Harrison's claim that 'we are appreciably nearer to the time when a serum test for syphilis will be routine in every medical examination' be made good in daily practice? The same writer speaks elsewhere of an investigation which he made into the cases of 280 women attending his clinic. Although their histories gave no reason for suspecting that they had been infected the serum test was positive in forty. Now, would the number of cases of unsuspected syphilis brought to light by these wholesale methods justify the trouble involved? It is clear that it would be quite impracticable to carry it out in a general practice, or even in that of a consultant not principally concerned with the treatment of venereal disease. It might, however, be found practicable to use it in the case of every one admitted to the wards of a general hospital, and indeed this has been done by Cowan and Faulds with the result that 8.6 per cent. of their male and 7.2 per cent. of their female admissions yielded positive reactions. Even this, however, might involve the pathologist and his staff in a good deal of fruitless work, to say nothing of the objections which patients are apt, not unnaturally

perhaps, to express to being punctured too often. The game is scarcely worth the candle, in the opinion of the writer. Indeed, it would seem that the routine use of the serum test need not be carried beyond its application to all cases of organic cardiovascular disease, so far as its value in searching out unsuspected cardio-aortic syphilis is concerned. If this be practised it will without doubt occasionally disclose a syphilitic element in the causation of cases where it might otherwise be overlooked; as, for example, in Lian's series where a positive reaction to the test appeared in 29 per cent. of 291 cases of hypertension. Few would claim that this implied a syphilitic basis for the hypertension; yet it does recall forcibly to one's mind the fact that the very people who suffer most from hypertension are also those who are likely to have syphilitic aortas. This view of the relation between syphilis and hypertension is confirmed by Horine and Weiss, who proved that the incidence of the former in cases of the latter depends on age and sex. Also it is well to recollect that ulcerative endocarditis of the aortic cusps, occurring in a middle-aged man, may be engrafted on a syphilitic basis. Sumbal, for example, found a positive Wassermann reaction in eighteen out of fifty-two cases of endocarditis lenta. It is, however, rare to discover a positive reaction in cases of rheumatic heart disease, for the two infections attack different groups of people and seldom overlap. Some examples of this rare coincidence have been elsewhere mentioned by the writer, and another example, proved by autopsy, has just come under notice.

Negative reactions, in cases which in other ways conformed to the diagnostic requirements of aortic syphilis, are recorded by Reid who got twenty-five positive and seven doubtful results from his Wassermann tests in forty-two cases, and also by Smith and Kimbrough whose percentage of negative tests was fifteen (identical with that of Hubert over a large series of cardiosyphilitic cases). Schlesinger found that the test 'left him in the lurch' in one-third to one-quarter of definitely syphilitic cases, and Wittgenstein's figures were similar. Negative reactions such as these, and also weakly positive reactions, may perhaps be encountered in patients whose infection has burnt itself out. Schlesinger alludes to these, saying that one sometimes sees post-mortem evidence of an unsuspected and obsolete aortitis. The writer has seen unmistakable evidence of this kind of thing in microscopic sections of the aorta from a man of 69, who died a cardiac death because he had, in addition to these residual lesions of syphilis, a widespread arteriosclerosis—a coincidence to which Schlesinger and other writers refer. In life this man's serum gave a weakly positive reaction to the Wassermann test. Parkinson quotes a somewhat similar case. But the obverse of this fact is that even if the syphilitic process has come to a standstill, the prognosis is not simply that of an obsolete infection, for the lesions which it leaves are of such a kind and distribution as to anticipate and then to reinforce the gradual decay of that aortic elasticity which is so vital a function of the arterial tube. This coincidence embarrasses the morbid anatomist in his diagnosis, for it is not always possible to discriminate with

the naked eye between aortitis and atheroma; though this difficulty can hardly be held to explain away so wide a discrepancy as that reported by Levine, who in forty cases of aortic syphilis (verified by autopsy) had twelve negative reactions to the serum test. Pathologists seem generally disposed nowadays to follow the teachings of Turnbull and Andrewes who could not satisfy themselves of any direct connexion between syphilis and diffuse arteriosclerosis.

It seems impossible to escape the conclusion that there is a considerable margin of error in the Wassermann test, almost wholly in the direction of negative reactions that ought to be positive. It is therefore a mistake to rely on this test alone to determine a diagnosis of cardio-aortic syphilis. The appropriate sequence is, as usual, that dictated by common sense: discovery of organic disease of the heart is followed by exploration of the anatomical pattern which that disease has achieved, and if this is not incompatible with a syphilitic ascription, the diagnosis of cardio-aortic syphilis may be made. This is powerfully supported if there is a history of syphilis, or if syphilitic lesions of the nervous system or other organs can be found; also, though only too rarely, if antisyphilitic treatment is obviously successful. Finally, it is also supported by the discovery of a positive reaction to the Wassermann test; but the absence of this reaction does not exclude the possibility of that diagnosis.

Treatment

So much has been written about the treatment of cardiovascular syphilis, and opinions vary so widely, that at first sight the task of bringing these together into any kind of conclusion looks impossible of achievement. Perhaps the best plan is to consider the matter as it appears in the different stages of the disease.

(a) *Effect of active treatment of early syphilis on liability to aortitis.* On this, three views are expressed. The first is that vigorous treatment will prevent the development of aortitis. Osler, for example, in the third of his Lumleian Lectures, went so far as to say, 'when a man gets a specific aortitis it means he has not had efficient treatment'. There are, however, those who express an exactly contrary view. Like Paré, who hinted that aortitis was caused by mercury, these writers believe that aortic lesions have become commoner since the introduction of synthetic arsenical compounds. Coenen, for example, compared a series of cases of central nervous syphilis examined *post mortem* during the six years immediately before the adoption of salvarsan, with a similar series in which it was probable that salvarsan had been used; and found that the percentage of those in the salvarsanized series was nearly twice as high as the other. A similar opinion is expressed by Schlesinger. A third point of view is that treatment makes very little difference either way. To quote Paré again, 'the lues venerea which now reigneth is far more mild and easie to be cured than that which was in former times whenas it first began

among us'. Astrologers, he says, see in this an operation of natural forces : but 'physicians had rather take to themselves the glory . . . and refer it to the many and wholesome means which have been invented, used, and opposed thereto by the most happy labours of noble minds'. In other words, any improvement that has taken place is perhaps due to the operation of natural causes. That careful and thorough treatment of the infection during those stages when it is open to treatment cannot guarantee immunity from aortitis, is proved by a case related by Symmers and Wallace ; that of a medical man who, in spite of 'intelligent antisypilitic treatment for three years' was found *post mortem* to furnish 'an exquisite example of syphilitic aortitis from commencement to bifurcation'. Similar cases are recorded by Gallavardin, and by Caussade and Foucart. This kind of experience is not unfamiliar to those who have had under their care many patients with this disease. On the other hand, if it is true, as Saethre and also Brunsgaard assert, that even in untreated syphilis the proportion of those who develop aortitis is not above 17 per cent., it would appear that this liability is not much greater than it would be among those who have been adequately treated. The question is one which, as has already been observed, is about to answer itself. The years that ended and followed the War were those in which the incidence of syphilis in this country apparently rose higher than for some time previously. This was met by a campaign of early diagnosis and thorough treatment. Did that treatment actually cut short the infection as it was meant to do ? Of this the incidence of aortitis as arising in those thoroughly treated persons should constitute a reliable index. It is not impossible to find out the numbers of patients who are at the present time being admitted to hospital for cardio-aortic syphilis. At any time from now on an increase in these figures is to be expected if the intensive treatment has failed, for the latent period needed for the development of diagnosable aortitis is fifteen to twenty-five years. It is much to be hoped that these data may be forthcoming.

In the meantime it cannot be doubted that it is right to treat syphilis thoroughly, to regard as a motive for this course the wish to prevent aortitis from developing. The fear lest treatment of this kind should increase the liability to aortitis is ill-founded. It depends on an assumption that does not appear to the writer to rest on sound evidence ; namely, the assumption that aortic syphilis is on the increase. It is more often diagnosed, both by clinicians and by pathologists, than it used to be ; and indeed it is probable that in both these fields lesions are labelled syphilitic on inadequate grounds. There is no doubt than in its grossest form, that of aortic aneurysm, this lesion is less common in our great general hospitals than it was. It is in fact disappearing slowly—though it would perhaps be going too far to agree with an experienced physician who recently expressed the opinion to the present writer that lectures on cardiovascular syphilis would soon have an historical value only, since the disease itself is becoming

obsolete—and all our experience of syphilis supports a belief that this decrease is in part due to an increase in the percentage of those who receive thorough treatment.

(b) *Effect of treatment on focal myocarditis.* That this group is small has already been shown. Yet it is definite, and one of its distinctive features is that cases which enter into this group respond to treatment. In this as in other respects, the clearest example of the focal kind of lesion is furnished by such lesions as cause auriculo-ventricular heart-block. Here good results are sometimes secured by the administration of potassium iodide, as in the example recorded by Keith and Miller. Complete recovery did not ensue, but there is little doubt that the course of the lesion was arrested; and this is similar to the experience of others who have treated the same kind of case in the same way. Perhaps the favourable accounts which the earlier writers on syphilis were able to give respecting their experiences of the action of drugs were due to the fact that in those days the focal lesions furnished a larger proportion of the cases of cardiac syphilis diagnosed as such, than they do now.

Another kind of syphilitic lesion of the heart-wall which responds to treatment by potassium iodide is that described by Gravier as 'subacute syphilitic myocarditis'. Cases of this kind are rare, and generalizations are therefore unwarrantable; but, in view of the remarkable cessation of serious and even dangerous symptoms which these patients may exhibit as a result of treatment, it seems justifiable to add these to the categories of those cardiopathies which, occurring in the earlier or haematogenous phase of syphilis, react more favourably than do the later lymphogenous lesions. As an example may be quoted the case of a man, aged 36, admitted to the Bristol General Hospital for pulmonary signs which proved to be syphilitic. While in hospital he became dyspnoeic and cyanosed, oedema was seen, his pulse became alternating, and a triple rhythm was audible. All these rather formidable evidences of a progressive myocardial lesion disappeared in two or three weeks under treatment with potassium iodide and mercury, followed by arsenic. Seen eighteen months later, he displayed no evidence whatever of myocardial disease.

In this more favourable group it does not seem possible to include other of the earlier syphilitic lesions of the heart; neither the aortic valvulitis of which Gallavardin and Gravier write nor the acute coronaritis recorded by Brooks and Lukomski. Records of such lesions are scanty, and the difficulty of recognizing their presence, or their syphilitic nature, or both, is so great as to nullify the prospect of achieving much by treatment.

Effect of Treatment on Aortitis

The conflicting character of the statements made by different writers on this subject, and the unsatisfactory nature of much that is offered in support of this, that, and the other plan of treatment, recalls to one's mind

the impression produced by reading, year after year, summaries of what has been said about the treatment of taboparalysis. In this group as in that, the failure to secure the results that are desired is admitted, not in so many words; but as frankly as if it were so, in the resourcefulness and ingenuity which clinicians show in devising new plans of treatment, for it is hardly to be supposed that this would happen if some perfectly successful plan had been discovered already.

It is proposed to limit this discussion to a consideration of means employed to combat the infection, and to omit from it the measures adopted to relieve the circulatory failure that ensues. Among these means the *iodides* may perhaps take first place, since there is little doubt that they are of some value. Most writers advocate their use in the early stages of treatment of aortitis. What is not so certain is their mode of action and the extent of the good they can do in this disease. The first is a matter for pharmacologists and need not be discussed here, though a remark made to the writer by the late W. E. Dixon, to the effect that the substance of a syphilitic granuloma melts if immersed in an aqueous solution of potassium iodide in a test-tube, provokes interesting speculations.

There is little precision in our knowledge of the applicability of this remarkable drug to the treatment of established syphilitic aortitis. An undeterminable fraction of the aortic lesion, that which is represented by the accumulation of inflammatory cells, is susceptible of improvement by the action of potassium iodide. It seems possible, for example, that the mere mechanical injury wreaked by these accumulations on the aortic wall as they collect between the elastic laminae, may be checked and limited by this means. There are writers who say that this action, by melting away the adventitial infiltrations, may weaken the aortic wall and thus do more harm than good. More, however, will be found to agree with Osler that the use of iodide relieves the pain of syphilitic aortitis. Rosin speaks well of the sodium salt pushed to the point of iodism and continued over many months. Cowan and Faulds commend Donovan's solution. Bullrich said that he used lipiodol if the iodide of potassium was not well borne, adding that he had found the tincture of iodine inactive. The writer had one patient, a medical man, who found that he tolerated iodine by inunction much better than iodide by mouth. Hift says that mercury, arsenic, and bismuth have superseded the iodine plan and made it superfluous. In general, however, the impression received from reading a number of papers is that most physicians who have treated these patients are content that iodide of potassium does real good. Whatever else is disputable, on this they are agreed; and most of them begin to give the drug as soon as the diagnosis is made, carrying on with it even if other methods are added.

Unfortunately, however, there is anything but unanimity with regard to the value of those substances which are thought to act by killing the spirochaetes; mercury, arsenic, and bismuth.

It is surprising to find how little is said in support of *mercury*. Lambert,

speaking in a discussion in New York on the paper by Moore and Danglede referred to below, looked back to the pre-salvarsan era and claimed that more than one generation would bear witness to the value of mercury in treating cardiovascular syphilis. Others leave it out of their plan of treatment altogether, using only arsenic or bismuth. Most writers mention it, but without laying stress on the details as they do in describing their usage of arsenicals or of bismuth. It is therefore all the more interesting to find Stokes pleading for a revival of its use. Several writers comment on the value of the mercurial diuretics, such as salyrgan and novasurol, in the later dropsical phases of the disease.

From the discussions of *neosalvarsan and the other organic arsenical compounds* three tentative conclusions seem to emerge. The first is that it is difficult to prove that these drugs exercise any delaying effect on the course of aortic syphilis. Hines and Carr got better results in aortitis than in aneurysm or aortic leak, but on the whole group think that they brought about symptomatic improvement in 57 per cent. of the cases so treated. Moore and Danglede claim that by beginning with bismuth or mercury, and the iodides, and following this by long courses of novarsenobenzol or bismarsen in small doses, they were able to achieve results that were definitely better than those seen in cases not so treated. The duration of life in aneurysm in the untreated cases averaged nine months from the onset of symptoms, as compared with sixty-nine months in those who had a year or more of treatment. In patients with aortic regurgitation and other forms of cardiovascular syphilis the treated patients lived sixty-five months as against thirty-two in the untreated. Conybeare also found that aneurysm patients treated with novarsenobenzol lived longer than those who were not so treated, and Pinard holds the same view. Hazen, on the other hand, discriminates between the results achieved in simple aortitis which he finds to be good, and those seen in persons who have developed aortic incompetence, or aneurysm, in whom no such relief is detected. Leschke stated that he knew of many private patients who, having undergone repeated courses of this treatment, were still alive and well more than fifteen years after the onset of symptoms. Cotton found that the average age at death was 45 in those treated with novarsenobenzol and mercury and 43 in those treated otherwise. Hift claimed that with such measures 75 per cent. of his patients were enabled to resume work. He, like others, is guided better, he thinks, by symptoms than by signs or serum tests in watching the course of the disease. The opinions that have been quoted here have been selected, not only because they are supported by evidence, but also because they represent the more optimistic view of these plans of treatment. There are, however, others who, like Fischer, declare that the results are disappointing, apart from the mere positive drawbacks to be considered below; and even if the more satisfactory figures stated above be accepted without reserve, they do not tell a very encouraging tale.

The second view that is to be found in many papers is that arsenical

treatment of cardiovascular syphilis is positively dangerous. Bullrich thinks it may make aneurysms worse. Doumer, Tixier, and Meyer describe examples of fatal cardiac failure to which they believe this treatment contributed, by provoking a Herxheimer reaction. This, as Cowan and Faulds remark, is a local as well as a general reaction, and patients with narrowed coronary orifices cannot afford even a transient exacerbation of this lesion. Fischer also holds that electrocardiographic evidence of coronary obstruction is an absolute contra-indication to arsenical treatment. Stokes says exactly the same thing. Donzelot considers that novarsenobenzol has been misused both by administration to cases of cardiovascular disease, the nature of which is doubtful, and by its use in persons with defective renal and hepatic functions. The view that this treatment involves definite risks is therefore widely held and adequately supported by evidence.

Thirdly, there are those who admit the risks and the disappointments that are inseparable from the use of neosalvarsan in cardio-aortic syphilis, yet advocate its use on the ground that it is the best means available. These writers all insist on the need for beginning with small doses and increasing them with the utmost caution. Many of them prefer to begin with mercury or bismuth, as well as the iodides, and gradually to introduce arsenic. All sorts of combinations of these remedies are proposed, but, so far as the arsenical preparations are concerned, no one seems to offer any plan more likely to suit the average case than that of Harrison who advocates long courses of small doses of novarsenobenzol given twice or even three times a week.

It is, doubtless, a sense of the limited value of the arsenicals in this disease that has led many to hope for better things from *bismuth*. Introduced ten years ago, it has now many advocates in all countries, one of the chief (as well as perhaps the first) being Levaditi. A general discussion of its merits is impossible here, but it seems from the published reports to be devoid of some of the risks attending the use of arsenic in cardiovascular syphilis. Probably, however, as its risks are less so also are its spirillicidal effects. Time alone can prove whether this drug is destined to supplant either arsenic, or mercury, or both, in the treatment of syphilis. Stokes thinks it a mistake to suppose that it will take the place of the organic arsenical compounds. These have now been in use for over twenty years, and yet no one is quite convinced that their introduction has decreased the liability of the syphilitic patient to develop late visceral lesions. Much less, then, is a trustworthy and final judgement of the value of bismuth to be looked for yet.

The broad fact that emerges from a consideration of all that has been written on these spirillicidal measures, and particularly on their capacity to cut the infection so short as to prevent the development of aortitis, is that nobody can prove that any drug possesses this power. It is certain that continued treatment is necessary if the infective agent of syphilis is to be prevented from inflicting slow but irreparable injury on the aorta; and

that it is most effective when it is early, i.e. when it is given while the spirochaetes are at large, and easily reached through the circulating blood. What is not so certain is the best means to employ. It is at least open to question whether the introduction of the arsenical mode of treatment may not have nullified its own beneficial results, at all events to some extent, by inducing a false sense of security. This danger is all the more real because the effect of treatment is too often gauged by the behaviour of the complement-fixation test, and by this alone. Whether the arsenical treatment, so conducted, has succeeded or not will soon be known; for if the campaign against syphilis, which has employed this as its chief weapon, should prove to have prevented that increase in the incidence of aortitis which we might otherwise expect within the next decade, then it will have gone far to make good its claim to be a *therapia sterilisans magna*. Even so, however, some allowance must also be made for the influence of an improved standard of education which induces the syphilitic patient to seek treatment earlier, and to carry it on longer, than he was used to do in former times.

In sum, then, the treatment of cardiovascular syphilis is that of syphilis itself. From the moment of diagnosis of the initial lesion the duty of the medical man in charge is to maintain an attack on spirochaetes; and it is probable that the best results will be achieved if this attack be renewed from time to time throughout the patient's life, even if neither symptoms nor signs nor serum reactions indicate any active infection. And if, unhappily, evidence of cardiovascular disease should develop notwithstanding, this should be attacked by potassium iodide, and by either arsenic or mercury or bismuth. Arsenic should not be given if there is evidence of an advanced aortitis; if the aortic valves are already leaking, then arsenic should only be given in small doses, and, if there are signs of coronary stenosis, it should not be given at all. In its place mercury may be given, or bismuth if the judgement of the medical man leads him to prefer it. From that time onwards, treatment by potassium iodide, together with one or other of the spirillicides, must be maintained, except for the intervals that are needed to detoxicate the patient and to give him a rest from time to time.

Conclusions

The heart and great vessels show evidences of attack by syphilis (*a*) during or soon after its earlier blood-borne phase, (*b*) at an interval of one, two, or more decades after the primary infection. The second group is many times larger than the first, and much less amenable to treatment. In this latter fact, as well as in the delayed and insidious manner of its origin, these later lesions resemble those of taboparalysis. The aortic inflammation which is the chief feature of this group is apparently provoked by irritation reaching the aortic wall through lymphatic channels. There are reasons for

thinking that the source of this trouble lies in the mediastinal lymph glands, and that these act as reservoirs of infective material. By the time this material has spread from the lymph glands to the aorta in quantity sufficient to cause changes appreciable to the clinical observer, the damage done is already considerable and largely irreparable.

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THE RELATIVE VALUE OF SOME DIPHTHERIA PROPHYLACTICS; AND THE PRINCIPLES OF ACTIVE IMMUNIZATION AGAINST DIPHTHERIA¹

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1. *Introduction*

THIS paper may be read as an appendix to the review on 'Schick's Test and its Applications' which was published in this Journal in 1928-9 (1), from which discussion on the use of diphtheria antigens in practical preventive medicine was purposely excluded. When comparing the immunizing power of two or more preparations it is desirable that the material each is tested on should have the same original 'immunizability'. In 1922 (2) it was proved that the longer a boy had been in residence at Greenwich Hospital School (in future abbreviated to G.H.S.), the greater was the probability of his having a negative Schick reaction. Further, in 1928 (3), when the whole school was being immunized, it was discovered that, on the average, new entrants took longer to immunize artificially than boys who had been some time in G.H.S. In short, in this environment, where diphtheria had been exceptionally prevalent, both Schick 'herd immunity' and 'herd immunizability' increased with length of residence in school.

Many observations from all over the world support the theory that Schick immunity is produced naturally by the toxigenic diphtheria bacilli in the environment, and thus the frequency of negative Schick reactions, in any natural group, is an index of its past experience of diphtheria bacilli. In turn the degree of Schick immunity of a group is also an index of the 'immunizability' of the positive Schick reactors of that group. Therefore, in comparing the antigenicity of two or more diphtheria prophylactics, it is advisable that the susceptibles they are tested on should come from groups having the same original Schick reaction frequencies. In this respect the new entrants to G.H.S. formed good material, since, as is shown in Table I, the positive Schick frequency, of each batch rarely varied significantly from 57 per cent. Secondly, since the rate of acquiring *natural* Schick immunity is a function of the environment, it is preferable in comparing two *artificial* antigens that the groups employed should, during the time of their immunization, live under identical conditions, especially as regards risk of exposure

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to infection with virulent diphtheria bacilli. The new entrants to G.H.S. satisfy this requirement, as far as is ever possible when using man as an experimental animal. And, although at G.H.S. the carrier rate for toxigenic diphtheria bacilli was variable, yet it did not show any very marked or frequent deviations from 3 per cent. during the period of investigation. Although these two factors, original immunizability and exposure to the natural antigenic stimuli in an environment, are theoretically of importance, yet, relative to the strength of the artificial prophylactic and the time it is allowed to act, these factors can generally have little weight in determining the proportion of Schick susceptibles who will ultimately acquire immunity as the result of a course of strong diphtheria prophylactic; because, as a rule, natural active immunization is so much slower and less intense than artificial.

2. *Toxoid versus 'Floccules'*

As the material at Greenwich was limited, it was decided to neglect toxin-antitoxin mixtures, and to compare the value of toxoid and toxoid-antitoxin floccules as practical prophylactic agents. Toxoid (and Ramon's anatoxine) is diphtheria toxin which has been treated with formaldehyde until it loses its toxicity but retains its antigenicity. 'Floccules' is the washed and resuspended precipitate which forms when toxoid and diphtheria antitoxin are mixed as described by Glenney and Pope (4).

The results of the different prophylactic courses which were given to each batch of the new entrants to G.H.S. are shown in Table I. On the left-hand side of the table are given the numbers of boys who remained Schick susceptible at retests, approximately one, two, three, and six months after their first prophylactic injection. The prophylactic courses generally consisted of two doses of antigen followed by a Schick test—further doses were given to the residual positive Schick reactors found at each retest. The courses were variable, but the number of inoculations, and the length of the intervals between them, are given on the right-hand side of Table I. A few boys who, from sickness or for some other reason, fell out of line in the routine courses were omitted from Table I. All these excluded subjects were successfully immunized at irregular intervals, and none call for any special comment. Table II, which is condensed from the data in Table I, shows the percentage of groups to acquire Schick immunity, at the indicated intervals, after the start of their prophylactic courses. These courses are put down in order, from that giving the best, to that giving the worst result, according to the Schick tests which were done three months after the first prophylactic inoculation.

'Weak toxoid' was toxoid diluted 1 in 10. Only 62 per cent. of the samples, who got two doses of this prophylactic, became immune within three months, whereas, in the same time, the weakest of the three concentrations of 'floccules' which were employed immunized 86 per cent. of their group. Full strength English toxoid and the most concentrated

TABLE I

G.H.S. New Entrants. Decline in Schick Susceptibility.

Month of Entry.	Per cent. total entry Schick Positive.	No. Schick Positive Start of Course.	No. Residual Schick Positive. Months after first injection.				Type of Antigen.	Weeks Interval Between Doses.	
			1	2	3	6		1st and 2nd.	2nd and 3rd.
Jan. 1928	68 ± 3.8	20	16	12	6	3	W.F.	3	12
"	"	24	19	14	10	5	W.T.	3	12
April 1928	43 ± 4.4	14	—	7	2	1	W.F.	3	15
"	"	14	—	9	7	2	W.T.	3	15
June 1928	66 ± 5.7	18	—	11	4	3	W.T.	2	10
Sept. 1928	60 ± 4.3	38	—	14	2	1	W.F.	2	10
Oct. 1928	57 ± 4.3	17	—	10	1	1	W. ₂ and M.F. ₁	3	10
"	"	17	—	7	0	—	W. ₁ and M.F. ₂	3	10
Jan. 1929	52 ± 4.6	5	2	2	2	0	A.F. (a)	14	10
"	"	5	3	1	0	—	A.F. (b)	14	10
"	"	15	9	8	6	2	M.F.	14	10
Feb. 1929	57 ± 4.7	28	22	18	9	2	A.F. (a)	10	10
April 1929	62 ± 4.3	18	15	—	3	1	A.F. (b)	2	3
"	"	19	10	—	0	—	S.F.	"	"
May 1929	60 ± 4.6	30	21	—	6	3	M.F.	"	"
Sept. 1929	48 ± 4.2	20	12	—	2	0	'Ramon'	"	"
Oct. 1929	57 ± 4.3	41	30	—	2	0	S.F.	"	"
Jan. 1930	61 ± 4.3	36	14	—	0	—	S.T. (a)	"	"
Feb. 1930	54 ± 4.5	29	15	—	2	0	S.T. (b)	"	"
Total	57 ± 1.2	408	—	—	64	24	—	—	—

Types of antigen. F. = toxoid-antitoxin floccules. T. = toxoid. 'Ramon' = French toxoid. W. = weak. M. = medium strength. S. = strong. A. = Alum.

TABLE II

G.H.S. New Entrants. Increase of Schick Immunity.

Prophylactic Course.	No.	Per Cent. Immunized : Months After First Injection.			
		1	2	3	6
Strong toxoid	65	55 ± 4.2	—	97 ± 1.4	100
" floccules	60	33 ± 4.1	—	97 ± 1.5	100
Mixed "	34	—	50 ± 5.5	97 ± 2.0	97 ± 2.0
'Anatoxine'	20	40 ± 7.3	—	90 ± 4.5	100
Weak floccules	72	—	54 ± 3.9	86 ± 2.8	93 ± 2.0
Alum + floccules	18	17 ± 5.9	—	83 ± 5.9	94 ± 3.7
Medium "	30	30 ± 5.6	—	80 ± 4.9	90 ± 3.7
Long interval dose	53	32 ± 4.3	45 ± 4.6	68 ± 4.3	92 ± 2.6
Weak toxoid	56	—	39 ± 4.3	62 ± 4.3	82 ± 3.4
Total Boys	408	—	—	84 ± 1.2	94 ± 0.8

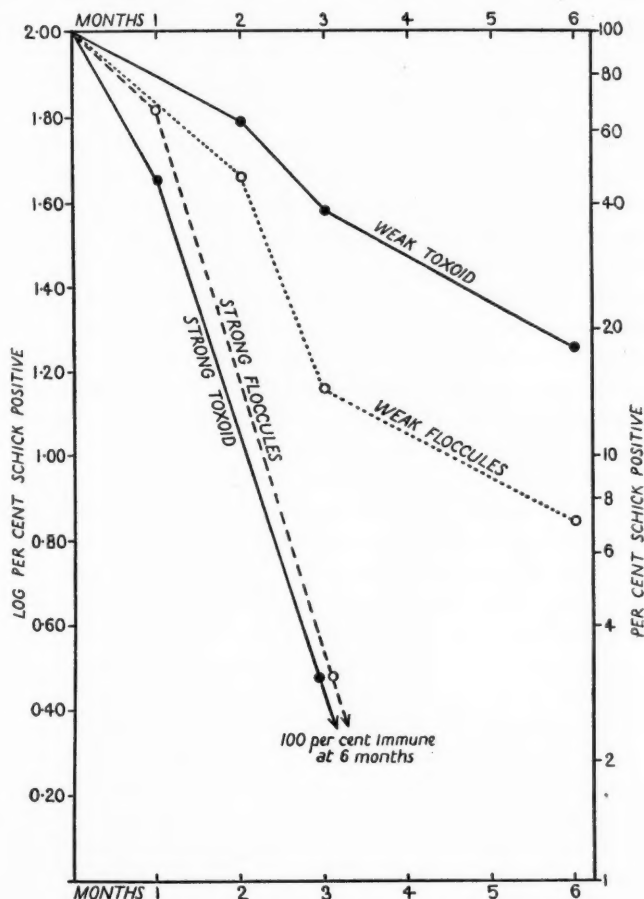
('strong') 'floccules' were both most satisfactory antigens. At three months there was no difference between them; both antigens had immunized 97 per cent. of the boys to whom they were given. It is noteworthy, however, that toxoid appears to act more rapidly than 'floccules' during the

first few weeks. Schick tests, performed a month after the first of two fortnightly inoculations, showed that a significantly greater number of the group of 'new' boys who had received toxoid were immune. The same phenomenon was observed when immunizing the 'old' residents of the school. Among the latter, Schick tests at one and two months made 'weak toxoid' appear the better prophylactic, but tests at three and six months showed 'weak floccules' to be superior to weak toxoid. This lag in the action of 'floccules' may have something to do with the fact that toxoid is a clear colloidal solution, while 'floccules' is a particulate suspension.

In comparing 'weak floccules' with 'strong', the data in Table II does not really tell us if, dose for dose, 'strong floccules' is the better antigen, because at three months the effects of three doses of 'strong' are compared with only two of 'weak'. As the figures stand 'medium' floccules appear to be not so good an antigen as 'weak'. This result is probably due to fluctuations in sampling; because, as will be seen later, 'medium floccules' successfully immunized subjects who were refractory to other antigens, and, moreover, a course of mixed doses of 'weak' and 'medium floccules' was as successful as any. This mixed course (see October 1928, Table I) was given to 34 boys, 17 of whom had a first and second dose of 'weak', followed by a third of 'medium', and 17 had one of 'weak', followed by two of 'medium floccules'. The batch of boys to whom Ramon's anatoxine (French toxoid) was given was too small to indicate whether its antigenicity differed from English toxoid. Similarly with the course labelled 'Alum and floccules'. Alum is supposed to have the property of prolonging the time after injection that a diphtheria prophylactic will continue to stimulate immunity. Therefore, 'alum and floccules', with 'medium floccules' as a control, were used to see how much Schick immunity could be stimulated by a single dose of prophylactic. It is seen in Table II that only 68 per cent. of the group used in this experiment acquired immunity in three months. This would not be good enough in practice, so at present there is little hope of being able to produce an effective herd immunity to diphtheria with only one injection—the ideal prophylaxis for which the public health administrator at present sighs in vain.

The rate at which a *course* of diphtheria antigen changes positive into negative Schick reactions is probably the best index of its efficiency. The rate is best envisaged by use of a semi-logarithmic diagram such as that on p. 217. In such a diagram the slope of the line (i.e. the tangent of the angle the graph makes with the horizontal) joining any two points of reference is directly proportional to the rate in the decline of Schick-positive frequency, during the period represented by the horizontal distance between the two points in question. The diagram shows that two doses of 'weak floccules', according to this form of measurement, were twice as powerful as two doses of 'weak' toxoid during the period of three months following the first inoculation. Over the same time, the rapidity of the action of three doses of 'strong floccules', and of three of full-strength toxoid, was equal, and each

of these antigens was twice as powerful as 'weak floccules'. The diagram also envisages the lag in the immunizing action of 'strong floccules' during the first month, where the slope of its graph is only half the slope of the graph representing the decline of susceptibility in the group which had



received strong toxoid. A last point worth noticing in the diagram above is that, between three and six months, the graphs for the two weak antigens are parallel, indicating that during this period the rates of immunization were equal. This phenomenon is probably caused by the presence of Schick susceptibles who are especially refractory to active immunization. This subject will be dealt with in the next section; but it may be noted here, that, as Tables I and II show, the numbers of residual positive Schick reactors, left three months after the start of the various prophylactic courses, was generally so small, that the chance presence in a batch of new entrants of only one boy, who was especially refractory to diphtheria

antigenic stimuli, would have a relatively enormous effect on the rate of immunization between three and six months. Therefore the rate of immunization in a group, after three months, probably depends as much on chance inclusion of one or two extra refractory subjects in the small batches of new entrants as on the strength of the antigen, provided the same prophylactic has been used throughout the whole course.

3. *The Refractory Schick Susceptible*

When any large enough group of subjects are immunized there will always be some individuals, even when three doses of the best prophylactic are used, who will resist acquiring Schick immunity for a disproportionately long time; and some of these may never become immune without further antigenic stimuli. The more intense a prophylactic course, the fewer the residual Schick susceptibles found at any specific time after its commencement; but, because especially refractory subjects will tend to accumulate more quickly in the susceptible residue, the *rate* of immunization after a certain time may become slower among the subjects receiving the more powerful immunizer. Thus after three months only 10 subjects (14 per cent.) in the group who received 'weak floccules' were left susceptible, but 21 (38 per cent.) who had received weak toxoid at the same time remained Schick positive. During the next three months, 5 of the first group, and 10 of the second, acquired negative Schick reactions. In this period, therefore, the rate of immunization (50 per cent. per three months) was equal (see diagram on p. 217). But it is obvious that, during this period, 'floccules' was being asked to do a harder task than the weak toxoid in immunizing a more refractory sub-group of positive Schick reactors.

Table I shows that 24 new entrants resisted active immunization for more than six months; to these may be added 16 boys (not shown in Table I) who had been resident for some time in the school, and who had remained susceptible for six months after starting a similar course, of weak toxoid or weak 'floccules', to that given to the new entrants of January 1928. These boys form a group of 40 refractory Schick susceptibles. The 8 new entrants of January 1928 and the 16 residents together form the six months susceptible residue of two equal groups, one of which had had three doses of 'weak toxoid', the other three doses of 'weak floccules'. Fifteen of this total came from the sub-group who had had weak toxoid, and these were given a fourth dose of the same antigen. The remaining 9 got a fourth dose of weak floccules. At a retest two months later, only 2 (13 ± 6 per cent.) of the former, against 6 (67 ± 10 per cent.) of those who had 'floccules', became immune—further evidence of the superiority of 'weak floccules' over weak toxoid. The remaining 16 susceptibles (combining both groups) were all given 'weak floccules' as their fifth dose of prophylactic, and another Schick test found that 9 were still positive reactors. These 9 formed the residual susceptibles from among 243 boys who had

received their first dose of prophylactic a year previously. They had resisted 5 injections of a weak prophylactic and 6 Schick doses of diphtheria toxin. They were now given a more concentrated antigen—'medium floccules'; and an eighth Schick test two months later found that all but one had become Schick immune—12 and 14 months after the start of their course. The fact that 8 of the 9 most refractory individuals had finally developed immunity within two months of receiving 'medium floccules' is striking evidence that it was really a more powerful antigen than 'weak floccules'. Also 14 of the remaining 16 'refractory' Schick susceptibles, found among the boys who joined G.H.S. between April 1928 and May 1929, all became immune, within nine months of their first prophylactic inoculation, after one or two doses of 'medium floccules'. These two exceptions, and the final survivor of the January 1928 batch of new entrants, deserve special mention. The latter received 3 doses of weak toxoid, 1 of 'weak', and 3 of 'medium', 'floccules' and 10 Schick tests, before acquiring immunity 18 months after the commencement of his prophylactic course. One of the others was finally immunized in 15 months, with 3 doses of 'alum floccules', 3 doses of 'strong' floccules, and 7 Schick tests. The last boy had the record resistance; he was given 9 inoculations (3 'weak', 3 'medium', 1 'alum', and 2 'strong' doses of floccules) and 11 injections of Schick toxin, before a twelfth Schick test was found negative, 22 months after his first inoculation. These three exceptionally resistant subjects show that it is improbable that any one is wholly incapable of producing circulatory diphtheria antitoxin if the antigenic stimulus is sufficiently intense and prolonged. On the other hand they prove that a few people must be born with a very low potentiality of acquiring circulatory antitoxin, i.e. they have a defect in their hereditary immunizability. Such low degrees of immunizability probably indicate a special susceptibility to severe diphtheria. If so these individuals become a difficult problem in practical active immunization, because, outside an institution such as G.H.S., one really cannot give twenty-one injections, distributed over nearly two years, to the child of even the most long-suffering of parents. Fortunately, however, the exceptionally resistant subject disappeared at G.H.S. with the institution of three doses of strong antigens at fortnightly intervals (see Table I, September 1929 to February 1930). Since I terminated my investigation in February 1930, I have learnt from my successor, Surgeon-Commander T. C. Patterson, that some 200 further new entrants have been given three fortnightly doses of a strong antigen (chiefly English toxoid), and no boy has resisted immunization for over nine months, though a few subjects have required one or two extra inoculations.

4. *English versus French Toxoid*

The work at G.H.S. demonstrates little if any difference in the antigenicity of 'strong' English toxoid and 'strong floccules'. But, owing to the success of Ramon's anatoxine in France, it is most important to

know if English toxoid is as good as French. According to Ramon (5), 96 per cent. of Schick susceptible French children acquire immunity within six months of the first of three injections of French toxoid (anatoxine). This frequency is practically the same as that observed at G.H.S. with full-strength English toxoid. But Ramon's groups must have largely consisted of children who came from communities in which the proportion of natural Schick immunes was lower than among the Greenwich new entries. In such a case the French susceptibles would have had the lower original 'immunizability'. Therefore, theoretically, the 96 per cent. of successful immunizations due to French toxoid would indicate a higher antigenicity than the same percentage caused by English toxoid in G.H.S. boys. Martin, Loiseau, and Laffaile (6), however, immunized an institution in which the original percentage of Schick susceptibles was 58 ± 1.3 , which indicates an 'immunizability' practically identical with that of the G.H.S. new entrants. With the usual course of Ramon's anatoxine 94 ± 0.8 of the positive Schick reactors in this French institution acquired immunity within three months. Therefore, as far as can be judged, the immunizing powers of French and English toxoid are equal.

5. *Toxoid versus Toxin-antitoxin*

The reports of the immunizing power of Ramon's anatoxine (toxoid), in the French medical press, were so much better than the results of toxin-antitoxin mixtures as recorded in American literature, that, before my own experience of English toxoid (full strength), I thought there must be a mistake somewhere: that is to say, owing to some difference in Schick testing, technique, or method of recording results, French toxoid could not really be so much better than toxin-antitoxin as it appeared to be on paper. Moreover, I was further confirmed in my scepticism by Park and Schröder (7) who, in 1928, suggested that there was no significant difference in the antigenicity of *average* toxin-antitoxin mixtures and *average* toxoid, and that a good toxin-antitoxin mixture was better than a bad toxoid, and vice versa. Shortly after this pronouncement, the Dicks (8) in 1929 immunized two samples, one with *three* doses of Ramon's toxoid, the other with *five* doses of a toxin-antitoxin mixture. The former immunized 94 ± 1.6 per cent., the latter 82 ± 2.6 per cent., of the samples they were respectively tested on. This seemed to leave little doubt that, dose for dose, the French preparation was superior in antigenicity to the batch of toxin-antitoxin mixture employed. But the Dicks' paper remained open to the criticism that the original natural Schick immunity of the population that their samples came from, and the time that had elapsed before they were tested for immunity, are not clearly indicated. Nor does the Dicks' work completely refute Park and Schröder's suggestion that a variability in different batches of either prophylactic is sufficient to account for the reported differences in rate of immunization. However, a careful piece of

work by Harrison (9) in 1930, definitely settles the matter and practically proves that any toxoid is a better agent for stimulating Schick immunity than any toxin-antitoxin mixture. Within four months *two* doses of toxoid immunized 95 ± 0.7 per cent. of the positive Schick reactors from a group of children originally 61 per cent. immune. Five batches of commercial toxoid were used, and all showed practically the same antigenic effect. In the same time *three* doses of toxin-antitoxin only immunized 64 ± 1.7 per cent. of the Schick susceptibles from a group originally 71 per cent. immune. Six batches of toxin-antitoxin were used; all, except one, which was very weak, showed approximately the same antigenicity. Thus with dosage and original immunizability in favour of toxin-antitoxin, any batch of toxoid immunized about 30 per cent. more children than any batch of toxin-antitoxin.

It is also significant that the antigenicity of toxoid, as measured by the Dicks on adults, and Harrison on children, is practically the same as that reported by Ramon and at G.H.S. Thus five sets of statistics from France, America, and England show that 94 to 97 per cent. of Schick susceptibles, whether adults or children, who received toxoid became negative Schick reactors within a few months. With the use of this prophylactic at full strength and in three doses, neither environment, place of manufacture, nor original immunizability can have much weight, in the rate of immunization of a group, compared with the antigenic properties of toxoid itself. The effect of 'herd immunizability', which is so definitely shown in Zingher's (10) and the G.H.S. statistics, and which I used to think of considerable practical importance, is not evident in Harrison's (9) data. His Schick susceptibles came from age groups of widely diverse Schick frequencies, yet, within the limits of sampling fluctuations, the old and young were found to have immunized at the same average rate when retested after four months. However, at G.H.S., at the time when differences in the rate of immunization were obvious, the antigens employed were weak, the inoculated groups were always re-Schick tested before more than half the subjects had had time to develop Schick immunity, and finally, just before the observations on immunizability, the intensity of the *natural* antigenicity of the Greenwich environment was higher than any other which is recorded in the literature. It would seem, therefore, that, in general, the intensity of artificial is so much greater than natural immunization that, after the lapse of four months, the effects of any differences in original immunizability may be swamped, or masked by sampling fluctuations among the small number of individuals who remain Schick susceptible after four months. This point is important because it means, provided the immunizing power of a diphtheria prophylactic is as strong as toxoid, that, in practice, one need not bother about the original natural 'immunizability' of a group.

To summarize, toxoid is a much more powerful antigen than toxin-antitoxin mixture. Moreover, with the latter there are possible, even if not very probable, dangers or inconveniences, due to the presence of unmodified

diphtheria toxin and horse serum. Therefore, all things considered, toxoid should take the place of toxin-antitoxin for routine active immunization against diphtheria, and the latter antigen be permanently relegated to an honourable place in the history of preventive medicine.

6. *Reactions after Toxoid and 'Floccules'*

What constitutes a mild, severe, or indeed any, reaction varies so much with the observer that it is hard to make fair comparisons of the reaction-producing tendencies of different prophylactics. At G.H.S. a local reaction was defined as any area of redness and swelling at the site of inoculation exceeding 3 cm. in diameter. After the first 250 inoculations with 'weak floccules' given at G.H.S., three boys had a minimal local reaction, without any constitutional disturbance. 'Medium' and 'strong floccules' showed no greater tendency to be followed by reactions than 'weak'. In fact, more than 1,200 inoculations of different batches of 'floccules' have now been given at G.H.S. without a single boy standing off duty for a day. If we define as 'practical' any reaction which causes an interference with the subject's ordinary avocation, then, in this age group (11-14) and environment, 'floccules' caused no 'practical' reactions. However, this complete freedom is not found when older age groups are given 'floccules'. Swyer (11), whose material was fever-hospital nurses, reported that eighteen local reactions (five with constitutional symptoms) and seven general reactions without local lesions followed the inoculation of 'floccules'. He only describes one reaction as 'severe', but five cases vomited. As far as can be gathered from Swyer's data, 11 ± 1.4 per cent. of his inoculations were followed by reaction. It was such rumours of reactions in adults that made the almost complete absence of reactions at G.H.S., after inoculations of 'floccules', hard to believe, so I asked Dr. R. A. O'Brien and Dr. C. C. Okell of the Wellcome Research Laboratories, from which both *Swyer* and *G.H.S.* obtained their *diphtheria prophylactics*, to examine sixty boys who had been inoculated the previous day with three different batches of 'floccules'. There was only one boy who showed any mark at the site of injection, other than the puncture of the hypodermic needle, and, although this was entered as a reaction, yet the visitors did not think it was worthy of record. The contrast between the hospital nurses and Greenwich schoolboys is doubtless largely caused by their age. Adults, as a rule, are always more prone to be protein sensitive to diphtheria antigens than children; moreover, if, as I believe, this hypersensitiveness is nearly always a specific bacterial allergy secondary to contact with the proteins of *B. diphtheriae*, then fever-hospital nurses should be more likely to give reactions after antidiphtheria inoculation than other adults.

The reactions following toxoid preparations are more frequent, age for age, than after 'floccules'. At G.H.S. the first 127 boys who received a dose of weak toxoid produced 13 (10 ± 1.8 per cent.) local reactions, 4 of

which were accompanied by a mild constitutional disturbance. Full strength English toxoid caused 14 (15 ± 2.5 per cent.) reactions among the first 96 inoculations. None were severe, but their intensity on the average was greater than those produced by weak toxoid. In general, increasing the dose of the same type of antigen does not have so great an effect in increasing the frequency of reactions as in increasing their intensity, when other conditions, especially the age of the inoculated subject, remain the same. English toxoid in Greenwich boys (aged 11 to 16) caused about as many reactions as 'floccules' did among hospital nurses.

A small batch of Ramon's French toxoid was obtained to compare its irritant effects with those of English toxoid. Only 51 inoculations of this preparation were given at G.H.S.; 23 (45 ± 4.7 per cent.) were followed by a local reaction more than 3 cm. in diameter. On the average these reactions were more intense than those seen after the English toxoid, and a few boys had to be 'put sick' for a day. One boy had a reaction which might be called severe; his upper arm and shoulder were red, brawny, and tender (area about 10×15 cm.). He had some constitutional disturbance (temperature 100.4° F.), and was stood off duty for four days. This was the most severe reaction following a diphtheria prophylactic ever seen in G.H.S. This batch of French toxoid was definitely more irritant than the English preparations thus far employed at Greenwich. Again, these reactions after French toxoid in boys must have been considerably less severe than those produced in adults; because in the Dicks' (8) sample of 100 subjects, who were given French toxoid, two-thirds were over the age of 18, and 76 ± 3.0 per cent. of the inoculations were followed by a reaction of some kind, the majority of which were mild; but a few are described as being accompanied by vomiting, high temperatures, and extensive inflammation of the arm. The Dicks also used some commercial American toxoid and found that the reactions which followed were 'about the same as occurred after injections of the toxoid prepared by Ramon'. Harrison (9), who used five batches of American toxoid on children, states that he had no trouble with reactions, but he supplies no numerical details.

The subjects most prone to severe reactions after antidiphtheria inoculations are those who give pseudo- or protein-Schick reactions. Fifteen positive and pseudo-reactors were given full doses of 'floccules' at G.H.S. Eleven of these gave no reaction at all, and the remaining four only mild local reactions. Of four pseudo-reactors who were inoculated with weak toxoid, three gave marked reactions. This absence of severe reaction after floccules, in protein-sensitive subjects—who, though they develop Schick immunity quicker than the average (one dose of any antigen is generally sufficient), are sometimes liable to very severe symptoms after toxoid—is one of the most valuable properties of 'floccules'. It probably depends on the fact that 'floccules' contains only a small fraction of nitrogenous matter as compared with other diphtheria prophylactics.

To sum up, toxoid-antitoxin floccules apparently do not give 'practical'

reactions in children. Toxoid gives a few reactions in children of 10 to 15, but, according to French experience, rarely causes a severe reaction in children of pre-school age. In adults and protein-sensitive reactors, toxoid may produce very unpleasant symptoms, and to this class 'floccules' should always be given when available. Toxoid, however, is apparently never really dangerous, since Fitzgerald (12) says: 'About 600,000 persons have been vaccinated in Canada with toxoid without any serious sequelae having been observed.'

7. *Mass Immunization of the General Population*

It is certain that toxoid can rapidly induce Schick immunity in the majority of positive Schick reactors. Schick immunity, however, does not of necessity mean immunity to diphtheria. This question was discussed elsewhere (1), and there is no doubt that the natural, or 'artificial', negative Schick reactor has a high resistance to recognizable clinical diphtheria. He is, however, only slightly less susceptible to carrier infection than the positive Schick reactor. Also, admittedly on rare occasions, *B. diphtheriae* may cause mild, anomalous, and transitory throat lesions in Schick immunes. A remarkable proof of the efficacy of toxoid in protecting children from the effects of diphtheria toxin is furnished by a recent tragedy in Mendelin, S. America (13). Two doses of toxoid were given to 48 Schick-positive children aged 2 to 7 years. Thirty-eight days after the first inoculation these children were given 1.5 c.c. of pure diphtheria toxin in error for toxoid. Sixteen children died but 32 survived (26 without serious symptoms). Each injection of toxin contained 300 m.l.d. for guinea-pigs. Although the fatal dose for an unprotected Schick susceptible child is not exactly known, yet it is probably much less than 300 m.l.d., because, in another disaster at Baden, 6 infants out of 40 died after receiving only about 10 m.l.d. of diphtheria toxin. Moreover, a herd of 300 guinea-pigs weighs four times as much as a child of 5, so it is hard not to believe that the majority, if not all, the survivors of the Mendelin catastrophe owe their lives to their previous inoculations with toxoid.

It can be safely concluded that, for the individual, toxoid is an efficient safeguard against clinical diphtheria. Moreover, to-day it can also be taken for granted that in institutions, such for example as G.H.S. (see May and Dudley (14)), where the administrator has a free hand and the complete population under control, clinically recognizable diphtheria can be practically eradicated by artificial active immunization. But the question remains—is it a *practical* proposition to protect enough children in the community at large to reduce the morbidity, severity, and mortality from diphtheria to insignificant figures as regards public health? Fitzgerald's (12) report on the antidiphtheria campaign in Hamilton, Ontario, appears to supply the answer. Between 1905 and 1924 the incidence of diphtheria in Hamilton (population 129,000) never fell below 144, and averaged 284 per 100,000

per annum. Half-hearted efforts at active immunization between 1922 and 1925 had no appreciable effect on the general incidence. In 1925 an intensive campaign was inaugurated, and by 1927 the morbidity had dropped to 9 per 100,000 and remained there till the report was written in 1930. Some 26,000 children in the school and the pre-school groups were given three doses of toxoid during the campaign, and, judging from the population of Hamilton, this figure means that probably two-thirds of the age groups under 20 had been inoculated by the end of 1929. It would seem, therefore, that when a large enough proportion of the susceptible population has been protected, diphtheria tends to die out—perhaps because the dissemination of the bacillus becomes too difficult for clinical, if not for carrier, infection to maintain itself. As regards the latter, it would be most instructive to learn something about the carrier rates for diphtheria bacilli to-day in Hamilton. Thus the protection of a large enough majority seems able indirectly to protect the residual minority of susceptibles in the community. So much for a most successful campaign against diphtheria. It will now be instructive to examine another experiment in mass inoculation against diphtheria, which was not so successful, and which was reported by Seligmann (15). In Berlin the Schick susceptibility of school children was exceptionally high (78 ± 0.05 per cent.). Sixty-six thousand children, who had received two doses of prophylactic, had a diphtheria morbidity of 2.7 per 1,000, as compared with 7.5 among the uninoculated children. Subsequent Schick testing of adequate samples (a preliminary or subsequent Schick test was not routine) showed that only about 63 per cent. of the inoculated group had acquired Schick immunity—a reduction in susceptibility almost identical with the reduction in incidence. The two doses of the German antigen in a community with such a high frequency of susceptibles, and, therefore, a low 'immunizability', was obviously inefficient. One may note that two doses of this German prophylactic produced less increase in Schick immunity than one dose of the 'medium' English antigens (see Table II).

In the two other diseases where active immunization has been widely employed—small-pox and enteric fever, the prophylactic—even if it fails to prevent attack, definitely reduces the clinical severity and mortality: both attributes which are often of greater importance to the public health than mere incidence. According to Seligmann, the mortality and 'severity' in the children inoculated unsuccessfully against diphtheria was not significantly different to that seen in the uninoculated. Seligmann interprets this to mean that the prophylactic could have had no action in modifying the illness of these children. I do not think this conclusion justified, because from experience elsewhere, if not mere common sense, it would be expected that the more immunizable, though Schick susceptible, children would be the least likely to get severe or fatal diphtheria; and this group most probably formed the majority of those Berlin children who were protected from attack. This would leave unprotected just those children who were

likely to die or suffer severely if they contracted diphtheria. And, although the majority of those who got diphtheria in spite of being inoculated probably came from this class, yet the type of illness they exhibited was the same as in the totally unprotected group. Therefore, it is not unlikely that the clinical severity of these patients was less than it would have been had they not been inoculated. On the other hand, there is another interesting statistic in this Berlin report which suggests that Seligmann may have been wholly, or in part, correct in his conclusion and that, in many cases, if a dose of antigen is too weak to prevent attack, it is also incapable of influencing appreciably severity and fatality. A group of 22,000 children only got one inoculation. The incidence and type of illness in this group was the same as among the uninoculated. These cases form a sub-group where the 'prophylactic' (*sic*) obviously failed to stimulate any group immunity, either against attack, or against 'clinical severity'. It almost looks that, as in most other physiological reactions, there is a 'threshold' value for an effective antigenic stimulus. That is to say, a subject will give no immunity response unless the antigenic stimulus is above a certain intensity. This 'threshold' varies, of course, in different individuals, and, on the average, is highest in those subjects who ultimately get diphtheria. The one dose of prophylactic used in Berlin was below the minimum intensity necessary to provoke an effective response in 'potential' diphtheria cases. This hypothesis receives some confirmation from the observation that at G.H.S. very 'refractory' Schick susceptibles disappeared on the introduction of stronger prophylactics, and that the 'strong' antigens rapidly immunized subjects who had resisted several doses of the 'weak' antigens. It is possible, therefore, that, unless a diphtheria prophylactic is known to have produced Schick immunity, it may leave some positive Schick reactors as susceptible as they were before inoculation: an important argument in favour of employing a subsequent Schick test to make certain immunity has been stimulated. These remarks, of course, do not apply to the atypical cases of diphtheria which sometimes arise in Schick immunes. Such patients, though they have not been guarded against attack, have undoubtedly received benefit from their inoculations, because their symptoms, in the vast majority of cases, are mild and transitory (see May and Dudley (16)).

The sequence of events in Berlin is highly instructive; because, owing to a low herd immunity to, and high incidence of, diphtheria, and a prophylactic course which left a third of the inoculated still Schick positive, it was possible to get statistics of a partially protected group, living under the same conditions, exposed to the same risks of infections, and submitted to the same standards of diagnosis, as the unprotected members of the community. The Berlin results are really a valuable testimony to the efficiency of active immunization in preventing diphtheria, because the use of a prophylactic course of far too feeble an antigenicity, as judged by French and Canadian standards, was able to prevent two cases and two deaths out

of every three which were to have been expected had the group of inoculated Berlin children not been partially protected against diphtheria.

I cannot close this section without noticing another Canadian report by Ross and McKinnon (17) which appeared after this paper had been drafted. This work is especially reliable because the statistics were corrected, for age, for the monthly distribution of inoculations and diphtheria, and also for the irregular exclusion of certain subjects of lesser susceptibility from the groups receiving toxoid. Between 1926 and 1930, 27,209 subjects, aged 5-14, which comprised about a third of all the school children in Toronto, were given one, two, or three doses of toxoid. The expected number of cases of diphtheria in the inoculated groups were calculated from the observed rates among the uninoculated school children. The results of the analysis may be tabulated thus:—

No. of doses Toxoid.	Expected Cases.	Observed Cases.	Reduction per cent.
1	34	24	30
2	200	52	74
3	222	23	90
Total	456	99	83

There were four deaths from diphtheria among the children who had received one or two doses of toxoid, but none among those who had had three. This work confirms the German experience, since one dose was followed by little protection, but after two doses there was a fourfold drop in incidence. From the public health view-point, three doses were followed by the practical eradication of diphtheria from the group receiving them. It may also be fairly surmised, from Mays and Dudley's (16) experience at G.H.S., that the residuum of recorded diphtheria, left after the tenfold reduction in morbidity, consisted chiefly of mild transitory cases, or even of patients falsely diagnosed as diphtheria.

It is interesting to compare the antidiphtheria campaign in Toronto with that in Hamilton. In the former, only a third of the school children, and apparently no pre-school children, were protected, and there was no evidence that the total diphtheria morbidity had fallen. This suggests that the proportion of the school population, which had been immunized was too small to afford any indirect protection to the uninoculated. In Hamilton a larger proportion of school children were immunized, and relatively as many of the pre-school group were also protected, and the general morbidity of diphtheria fell to an insignificant figure. This contrast between these two Canadian towns emphasizes the supreme importance of inducing active immunity before the children reach the school age.

Finally, all these experiences combined teach the important lesson that, if ever active immunization is to eradicate diphtheria from the population at large, it is no good dallying with weak or diluted prophylactics in one or two doses. Three doses of a strong antigen must be the standard course in any scheme which discards the use of routine Schick tests.

8. *Some Principles of Practical Active Immunization against Diphtheria*

(a) *Age for inoculation.* The earlier the better, once the infant has lost any congenital antitoxin it might have had. The ideal time is, therefore, between twelve months and two years. As a rule, except in certain institutions, such for example as G.H.S. and fever hospitals, active immunization after the age of 10 is relatively uneconomical, because at this age it will have failed to prevent more than 60 per cent. of the morbidity, and 90 per cent. of the mortality, to be expected in most urban environments. Therefore, in principle, the youngest children should always be immunized first, and, when no more of them can be obtained, the next higher age group taken. Moreover, the earlier in life a subject is inoculated the less likely he is to give any reaction. Pre-school children are obviously the class the administrator most desires to protect, but unfortunately they form the hardest age group to get at.

(b) *Choice of prophylactic course.* Three doses of full strength toxoid or 'floccules' at fortnightly intervals. Toxoid should be employed for children, since its efficiency and innocuousness in the young has been extensively proved in France and Canada, and it is, moreover, much cheaper and easier to manufacture than 'floccules'. The latter should, however, be selected to immunize adults, and any subjects who are known to be protein sensitive.

(c) *The use of Schick tests.* (i) The use of a preliminary Schick test, besides being more rational in saving from unnecessary inoculation those already immune, enables protein-sensitive subjects who are prone to give marked reactions, and who are generally already immune, to be recognized. A preliminary Schick test will also economize time and material, provided that the proportion of positive Schick reactors exceeds 60 per cent. For example, without Schick tests, 100 children will receive a total of 300 injections. With Schick tests, and 60 per cent. positive, they would receive 100 Schick tests and 180 inoculations, total 280. In most environments the pre-school group will be more than 60 per cent. susceptible, and it therefore becomes economical of time and material to discard the primary Schick test; also in this group protein-sensitive subjects are less common. The urban school-age group will often be less than 60 per cent. Schick positive, and a preliminary Schick test then becomes an economy, more especially if the group is to be Schick tested again at the end of the course.

(ii) A Schick test, three to six months after the first inoculation, is advisable, in order to pick out the children who have not been successfully immunized and who, therefore, should have a further prophylactic course. Such subjects are probably the potential diphtheria cases of the future. Where only two-dose courses, or prophylactics weaker than toxoid, are used, the subsequent Schick test must not be omitted, as the Berlin experience

described above so clearly emphasizes. However, a practical experience of full-strength toxoid has made me less emphatic than I used to be on the necessity of a subsequent Schick test (Dudley (1)). As a matter of policy, when dealing with a general public where every extra injection, or attendance at an 'immunization clinic', may make it harder for the administrator to obtain the wholehearted co-operation of the children's parents, all routine Schick testing may be discarded when three doses of full-strength toxoid are used. In Hamilton, where this policy was employed, the campaign met with complete success. Such a scheme deliberately leaves some 5 per cent. of inoculated individuals with positive Schick reactions, whom one hopes may have gained some increase in resistance, and may be indirectly protected by the immunity of the rest of the herd. Although Schick tests may be discarded as part of the general scheme, adequate samples of the community should be tested to gain information concerning original immunizability of the population, and to make certain that the prophylactics in use are *immunizing* at least 95 per cent. of those *inoculated*.

When time, money, and prejudice need not be considered, a Schick test before and after inoculation is, in all circumstances, the most satisfactory and scientific procedure.

(d) *Organization and cost.* This aspect of active immunization against diphtheria was dealt with ably, more than four years ago, by Graham Forbes (18), who showed the enormous saving in health and wealth that could be effected if all the London school children were made Schick immune. Forbes, I think, did not lay enough stress on the fact that it is the pre-school, rather than the school, child that so urgently wants protection—perhaps because this class is so much harder for the administrator to deal with. But I believe, if the choice was possible between having either all the pre-school group immunized, or all the school group, the first choice would probably cause a greater ultimate decline in the morbidity and mortality of diphtheria than the second, at half the expense in time and material. Forbes estimated that the cost of immunizing the London school children in one year would be about £85,000 and allowed £70,000 for the purchase of material at current commercial prices. The raw material and apparatus for the manufacture of toxoid cost relatively next to nothing. To give three doses of toxoid to all the London children under 15 would require about 3,000,000 one c.c. doses or about 640 gallons. This quantity of toxoid ought to mean 'mass production' in a government laboratory, and then the cost, including the salary of an expert immunologist in charge, should be nearer £10,000 than £70,000. Forbes suggested that thirty experienced medical officers would be required to immunize the 600,000 London school children within a year; but, if it were decided to discard Schick tests, toxoid could be given by any one who could be entrusted to use a hypodermic syringe. A good administration might, therefore, make use of medical students or trained nurses to assist the local health officers, under

the guidance and direction of two or three medical men with special experience in Schick testing and active immunization.

(e) *The maintenance of immunity.* This is of great importance, for suppose diphtheria had been successfully eradicated by artificial active immunization, and that then the practice of inoculation fell into abeyance: in such circumstances the community might become open to an unprecedented outbreak of diphtheria, as the result of a new generation of children growing up without any artificial protection and without any *natural* latent immunization owing to absence of diphtheria bacilli in the community. That this is a real danger is suggested by Chesney's able report (19) on the diphtheria work at Poole. At Poole, for nine years prior to 1929, the diphtheria morbidity was low (0.57 per 1,000 per annum), about a fifth of that seen in London. In 1929 the incidence increased more than sevenfold and the Schick susceptibility among the school children was found to be 81 ± 2 per cent. Chesney (and I agree) attributed the high herd susceptibility, and in turn the high morbidity, to a low rate of natural latent immunization in the years of low diphtheria prevalence. This sequence of natural events at Poole is what is to be expected, if after effectively reducing, or eradicating, diphtheria by artificial active-immunization, the immunity is not maintained in the rising generation. It should be noticed that the point is more important in the prevention of diphtheria than of variola major, where to a great extent vaccination has fallen into disuse; because, once eradicated, variola major can be kept in check by drawing a sanitary cordon round any introduced infection, which is practically always 'visible'—missed cases and carriers of *major* small-pox being rare or non-existent. In diphtheria, however, 'invisible' or carrier infections, which are far more common than 'visible' cases, can slip through the best-designed sanitary barrier. Nevertheless, it is by no means certain that toxigenic diphtheria bacilli would disappear completely from a fully protected community. After three years' practical freedom from clinical diphtheria, carriers of toxigenic bacilli are still common in G.H.S. If even a few carriers persist, small outbreaks of diphtheria would be expected among the youngest age groups, whenever the maintenance of artificial immunity began to slacken. Such outbreaks would be a warning to public health authorities that a big recrudescence of diphtheria was possible unless they re-established an efficient scheme of active immunization. The maintenance of diphtheria herd immunity in the London area would necessitate the immunization of the 60,000 or so infants who annually enter the second year of life.

(f) *Opposition to active immunization.* In any preventive measure, the hardest task of the public health administration is to overcome the inertia, and even active opposition, of the people they are trying to protect, and to educate them to submit their children to prophylactic injections. In fact lay prejudice, or its unintentional exaggeration by public health authorities, is possibly the chief, if not the only, reason why diphtheria is still with us. Probably the strength of this opposition is overestimated. In any pre-

ventive medicine campaign, as in so many other crusades, the acquiescent subject says nothing; but a few energetic 'conscientious objectors' can usually make enough disturbance to create the impression that any procedure they dislike is almost universally unpopular. Of the 1,000 G.H.S. boys' parents who were circularized, less than 1 per cent. refused to have their children protected. It is admitted that here we are dealing with a selected sample from which it may be unjustifiable to judge the behaviour of parents in general. In Hamilton, however, enough subjects accepted inoculation to ensure the success of the antidiphtheria campaign. Chesney (19) stated that in Poole 'the response of the parents to the facilities offered was very gratifying'. Here is one medical officer, anyhow, who apparently found less obstruction than he expected. I would be rather surprised if more than 10 per cent. of the parents and guardians in an average English community objected to having their children inoculated against diphtheria, provided that the procedure, its objects, and advantages, were explained in a tactfully worded leaflet.

9. Conclusion

From the evidence in the literature and from experiments at G.H.S., it appears reasonable to believe that three fortnightly doses of a reliable toxoid, if given to only half the population under ten years of age, would reduce the incidence and mortality from diphtheria to an extent that would make active immunization a sound financial investment, besides being of benefit to the public health. If as many as 80 or 90 per cent. of children under 10 could be maintained Schick immune, I believe diphtheria would, for practical purposes, vanish within five years.

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OBSERVATIONS ON THE DISTURBANCE OF METABOLISM PRODUCED BY INJURY TO THE LIMBS¹

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As the result of an investigation into the mineral metabolism of patients with fractures of bones, the present writer (1930, 1931) found that in normally healing cases the metabolism of calcium showed but little change and that intake on the average balanced output. There was, however, a very marked and early loss of nitrogen, sulphur, and phosphorus, the main excretory path for these catabolites being the kidneys. The rate of loss reached a maximum from the second to the eighth day following the injury and then gradually declined. There was still a slight but continuous loss even after the lapse of one or two months. The S:N and P_2O_5 :N ratios suggested that the material being catabolized was probably mainly muscle. A catabolic loss of nitrogen, sulphur, and phosphorus also resulted from the injury of tissues other than bone. There did not appear to be any coincident increase in the non-protein nitrogen or inorganic phosphorus of the blood corresponding to the periods of increased catabolism noted in these cases.

The partition of the nitrogen and sulphur-containing catabolites demonstrated that the increase in nitrogen was due to a practically proportionate increase in the urea excreted and that the increase in sulphur was due to a slightly greater proportionate increase in the excretion of inorganic sulphate. While the excretion of ammonia fluctuated, that of amino-acids and uric acid generally rose. Ethereal sulphate tended to diminish slightly. Creatinine and neutral sulphur remained practically constant, any increase being in no way proportional to the total increase of nitrogen or sulphur respectively. Traces of creatine were observed, particularly during the phases of increased catabolism. The occurrence of a creatinuria in patients with fractured bones had already been noted by Hirst and Imrie (1928). Traces of heat-coagulable protein were also occasionally found, particularly during the time of the maximum excretion of the nitrogenous catabolites.

The present communication deals with certain other manifestations of the increased catabolism after injury, namely, the changes in body temperature, pulse-rate, and oxygen consumption corresponding with the changes in nitrogen metabolism.

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While considerable attention has been paid to the condition of wound shock, both primary and secondary, relatively little consideration has been given to the general occurrences in metabolism during the period of renewed functional activity and of repair which succeeds the initial depression resulting from wound shock.

Although it has long been observed that a slight general rise in body temperature and pulse-rate may accompany an aseptic wound, data clearly relating these disturbances to a condition of enhanced metabolism have not often been recorded.

Wertheimer, Fabre, and Clogne (1919) appear to have been alone in providing data concerning the output of nitrogenous substances in the urine in clinical cases both during the period of depressed functional activity and during the subsequent period of enhanced metabolism. They investigated the urinary output of the first twenty-four hours in cases of war injury and found an average excretion of 16 grm. urea nitrogen. They also found an increased output of acid and ammonia. Following the period of shock the elimination of urea was found by Wertheimer and his co-workers to continue at a high level for some time and to amount even to 27 grm. urea nitrogen in the twenty-four hours. Apart from these observations and some on the retention of nitrogen in the blood by Duval and Grigaut (1918) the present writer knows of no other work bearing on this aspect of human metabolism.

Experimental Data

The seven male subjects of these observations were generally in good health apart from their tissue injury. The injuries were in Cases 1, 2, and 3 accidental fractures of the long bones below the knee with varying degrees of soft tissue damage. Case 4 had a simple dislocation of the ankle. These four cases were all studied from the first or second day after admission to hospital for the injury. The next three cases were all studied both before and after operation. Case 5 was one of operation on the humerus for old fracture, a bony splint being removed for the purpose from the tibia. Cases 6 and 7 had knee-joint incisions under stavaine spinal anaesthesia for the removal of torn fragments of cartilage. Other anaesthetics were used with Cases 4 and 5, but none in the treatment of Cases 1, 2, and 3.

All these cases were allowed to select the quality and quantity of food-stuffs required from a prepared list. The intake of food as well as the intake of water was kept as constant as possible. Immediately on admission the injured cases were placed on a constant diet and collection of urine was made in twenty-four hourly lots. In those cases admitted for operation urine was collected one to two days prior to operation and on the fourth to sixth days of constant diet.

The methods of urinary analysis are similar to those described in previous papers (Cuthbertson, 1930, 1931).

Immediately on admission these patients practised breathing through a mouth-piece with nose clip. The basal oxygen consumptions were sub-

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sequently determined with the patients lying at complete rest, 12-15 hours after their last meal, and kept comfortably warm. Determination of the oxygen consumed and the carbon dioxide eliminated were made by analyses of the respired air collected in Douglas bags. The pulse-rate and axillary or rectal temperatures were determined at six hourly intervals in certain cases. For tabular purposes, however, only the morning and evening pulse-rates and temperatures have been recorded.

TABLE I. *Case 1*

Fractured malleolus of right tibia of man, aged 51 years, due to crushing injury. 'Shocked' on admission. No anaesthetic used for splinting.

Surface area 1.725 sq. m. approx.

Daily intake N = 10.77 gm.

The fluid intake was 1,450 c.c. daily. (In all cases this includes water bound in food-stuffs).

Day following Injury.	Vol. Urine. c.c.	T.N. Urine gm.	T.SO ₂ Urine gm.	Basal Oxygen Consumption c.c. per min.
				243
2	450	9.87		172
3	650	13.33	2.79	272
4	1050	15.22		307
5	1240	16.80		288
6	1500	20.58	3.81	259
7	1300	18.06		275
8	1460	18.69		277
9	1250	15.33		238
10	1890	10.08		284
11	1320	16.36		
12	1580	9.87		

TABLE II. *Case 2*

Fracture of both bones of right leg and tibia of left leg of man, aged 57 years. 'Shocked' on admission. Practically no displacement of the bone ends, but some radiating cracks, and bruising but no tearing of soft tissues. No anaesthetic used in splinting the fractures. On the ninth day the splint was reapplied. On the day following the patient felt indisposed and could not take his dinner. On the eleventh day a pulmonary complication was found to have developed—probably an infarction of lung.

The fluid intake was 1,870 c.c. daily.

Surface area 1.53 sq. m. approx.

Daily intake of N = 8.23 gm.

Day following Injury.	Vol. Urine. c.c.	T.N. Urine gm.	Basal Oxygen Consumption c.c. per min.	Temp. °C.	Pulse.
3	850	12.39	249	36.55	78
				36.33	84
4	640	12.07	229	36.11	74
				36.21	74
5	1490	31.39	217	36.15	80
				36.55	88
6	1500	30.66	259	36.11	80
				36.90	86
7	1850	18.79	236	36.33	78
				36.90	86
8	1280	23.20	220	36.33	73
				36.15	73
9	960	18.27	213	36.11	72
				36.11	80
10	1030	17.43	244	36.72	80
				36.90	78
11	1280	22.15	267	36.84	77
				36.84	82
12	1000	16.80	261	37.22	90
			246	37.78	84

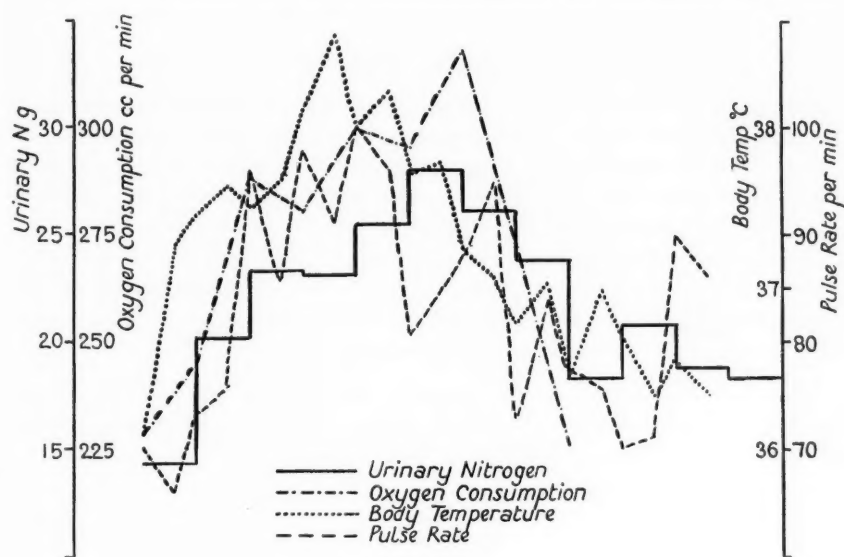
TABLE III. Case 3

Fracture of tibia of man, aged 34 years, due to kick on football field: some bruising: shock slight. No anaesthetic required.

Surface area 1.575 sq. m. approx.

Daily intake N = 15.36 gm.

Day following Injury.	Fluid c.c.		T.N. Urine gm.	T.SO ₂ Urine gm.	Basal Oxygen Consumption c.c.	R.Q.	Temp. °C.	Pulse.
	Intake (H ₂ O).	Output (Urine).						
1	1930	1070	14.28	3.03	228	0.805	36.11	70
							37.22	66
2	1930	1010	20.16		244	0.799	37.45	73
							37.62	76
3	2130	1240	23.31		288	0.765	37.50	96
							37.68	86
4	2130	1320	23.10		280	0.837	38.12	98
							38.56	91
5	2130	1300	25.51		299	0.788	38.01	100
							38.23	96
6	1930	1470	28.03	4.26	295	0.729	37.74	81
							37.78	85
7	1930	1520	26.04		318	0.690	37.22	88
							37.06	95
8	1930	1600	23.80		279	0.773	36.78	73
							37.12	84
9	1930	1190	18.27		226	0.785	36.45	78
							37.00	76
10	1930	1530	20.79				36.67	70
							36.33	71
11	1930	1390	18.79				36.55	90
							36.33	86
12	1930	1630	18.37					



Case 3.

TABLE IV. Case 4

Dislocation of ankle of man, aged 25 years; swelling but no discolouration of part. General anaesthetic for reduction.

Surface area 1.515 sq. m. approx.

Daily intake N = 12.67 grm.

Day following Injury.	Fluid c.c.		T.N. Urine grm.	Basal Oxygen Consumption c.c. per min.	R.Q.
	Intake (H ₂ O).	Output (Urine).			
2	1750	1530	11.06	254	0.713
3	2100	1280	10.08	246	0.626
4	1750	1220	14.70	264	0.734
5	1950	1450	16.66	244	0.682
6	1950	1710	19.74	265	0.644
7	1950	1630	18.48	277	0.657
8	1750	1220	14.28	305	0.712
9	1750	1330	12.88	306	0.546
10	1750	1560	17.92	310	0.677
11	1750	1800	17.72	266	0.656
12	1750	1720	16.10	271	0.733

TABLE V. *Case 5*

Man, aged 36 years, had old ununited fracture of humerus for six years. On constant diet for six days and then operation under chloroform and ether to splint humerus with bone taken from one tibia. During the first twenty-four hours following operation no urine was passed, and the patient's bladder was not distended. 23.41 grm. nitrogen were excreted on the day following, and this probably represents the products of the day of anuria and of the succeeding day. Probably the value 17.53 grm. found on the fourth day after the operation represents the real maximum output.

Surface area 1.59 sq. m.

For three days following the operation the patient was unable to take his full diet, but subsequently all was taken. With the exception of these days of reduced intake, the intake of fluid (H_2O) was 1,860 c.c. daily.

Day of Diet.	Vol. c.c.	T.N. grm.	Basal Oxygen Consumption c.c. per min.	R.Q.	Temp. °C.	Pulse.
			185	0.782		
3			220	0.772	36.72	81
4	1190	12.18	214	0.785	37.00	88
5	1350	11.86	227	0.852	36.67	81
					37.12	90
6	Operation.	No urine passed.			36.90	80
			201	0.773	38.12	100
7	1010	23.41	195	0.874	38.33	116
					37.67	98
8	590	12.70	226	—	38.23	108
					37.22	90
9	1300	17.53	214	0.861	38.12	104
					37.22	90
10	1090	9.86			38.01	100
					36.90	89
11	1380	13.33			37.78	100
					36.90	87
12	1280	11.23			37.00	92
					37.22	91
13	1500	11.65			37.06	92
					37.12	91

TABLE VI. *Case 6*

Man, aged 25 years, had knee-joint incision under stovaine spinal anaesthesia for removal of torn cartilage. Full diet not consumed during first 12-18 hours following operation. Note that maximum output of urinary nitrogen was more than double that of time before operation.

Surface area 1.65 sq. m.

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Fluid.		T.N. grm.	Basal Oxygen Consumption c.c. per min.	R.Q.	Temp. °C.	Pulse.
Intake (H ₂ O).	Output (Urine).					
1425	820	6.82	261	0.753	36.21	72
			260	0.654	36.44	76
Operation					36.21	68
					37.01	78
600	400	4.41	261	0.674	36.90	83
1050	900	13.75	291	0.559	36.73	81
1425	640	16.06	316	0.666	36.67	80
1825	650	9.76	263	0.756	36.78	84
1825	870	9.45	267	0.857	36.73	84
1825	1160	8.92	256	0.755	36.33	68
1825	920	8.61	259	0.807	36.11	68
					36.33	78
						79

TABLE VII. *Case 7*

Man, aged 21 years, had knee-joint incision under stovaine spinal anaesthetic for removal of torn cartilage. Constant diet continued throughout period of operation with the exception of breakfast on morning of operation. The maximum output of urinary nitrogen was more than double the output before operation.

Surface area 1.625 sq. m.

Fluid.		T.N. grm.	Basal Oxygen Consumption c.c. per min.	R.Q.	Temp. °C.	Pulse.
Intake (H ₂ O).	Output (Urine).					
			258			
			259			
1340	960	9.135	236	0.863	36.21	
			253	0.864	36.84	
Operation					36.33	78
					36.50	72
454	670	9.29	301	0.759	37.22	80
1540	1050	13.81	284	0.788	37.34	72
1440	1130	13.18	269	0.829	37.12	80
1540	1090	21.31	268	0.833	36.90	73
1540	1020	21.00	274	—	37.12	84
1540	1060	16.48	261	0.785	37.18	84
			243	0.847	37.12	80
					37.22	84
					36.90	77
					36.45	80
					36.45	77
					36.84	80
					36.33	78

Discussion

The effect of injury on body temperature and pulse-rate. The determination of the rectal temperature was impossible in the fracture cases owing to clinical conditions.

In general a febrile disturbance was noted in all these cases, but with few exceptions did it exceed $1-2^{\circ}\text{C}$. when determined in the axilla or mouth. This rise generally occurred within the first forty-eight hours following the injury and lasted for a day or two, although sometimes for as long as a week. There was almost always an increased pulse-rate, the general increment being ten beats per minute per 1°F .

The data of Case 2, Table II, indicate that a relationship exists between body temperature, pulse-rate, oxygen consumption, and urinary nitrogen. It will be noted that there was an initial period of depression followed by a rise in all the values.

The graph, Case 3, illustrates the marked disturbance of temperature, pulse-rate, oxygen consumption, and nitrogen excretion which followed the accidental fracture of both bones of one leg. It will be observed that the temperature, pulse-rate, and urinary nitrogen curves tended to run parallel and coincide in time. Although the rise in temperature preceded the rise in pulse-rate by more than twenty-four hours, this lag was eliminated later.

The graphic record of Case 6 again demonstrated the coincidence in time which the various fluctuations in body temperature, pulse-rate, basal oxygen consumption, and the urinary excretion of nitrogen may exhibit.

In Case 7 the data, when graphed, indicated that whereas the temperature and basal oxygen consumption curves ran parallel and coincided in time, they were of different form from, and preceded in time the increments in the pulse-rate and urinary nitrogen, which latter tended to coincide in form and time.

Reference to Case 5, Table V, will again indicate that an almost perfect correlation in time may exist between the fluctuations in body temperature (here determined rectally) and pulse-rate. In this case the oxygen consumption and urinary secretion were initially depressed.

Before discussing these relationships further, reference will now be made to certain cases whose urinary nitrogen excretion and basal oxygen consumption were determined daily from the second to third day following their respective accidents, but in whom no very accurate record of temperature or pulse-rate was made.

The effect of injury on the basal consumption of oxygen. These experiments cannot be considered ideal, since the subjects suffering from bone fracture were relatively unpractised in breathing normally into a Douglas bag, although they were made to practise frequently on the day of admission to the experimental ward. The first collection of expired air was made under 'basal' conditions at 9 a.m. on the morning following admission. The collection of urine commenced at 8 a.m. on the same day.

A distinct difficulty arose in the matter of correlation. In the case of

the total urinary nitrogen we are dealing with the summated effects of twenty-four hours' metabolism; in the case of the oxygen consumption we are arbitrarily selecting one small period of time in the twenty-four hours in which to assess the patient's metabolic level. Wishart (1928) in his interesting correlation between basal metabolism and the urinary excretion of nitrogen compared the twenty-four hourly excretion of nitrogen ending at 8 a.m. with the heat output as determined at that hour. It is the writer's view that a truer method of representation can be obtained by assuming that the twenty-four hours' excretion of nitrogen is intermediate in metabolic time between the basal consumption at the start of the twenty-four hours and the basal consumption at the end of the twenty-four hours. This plan has been adopted in the various tables, but in the graphical records the 'block' method has been applied to the representation of the urinary nitrogen.

The basal heat production has not been calculated in these cases since it was considered that the respiratory quotient could not be absolutely relied on, and further it was not possible to weigh these fracture cases. The approximate surface area has been recorded, from measurements made after convalescence. While the respiratory quotient of an unpractised person is generally above unity, it is interesting to note the relatively low values found in these cases of injury. Values below 0.7 were common.

Case 1, Table I. It will be observed in this case that whereas both the output of nitrogen in the urine and the rise in oxygen consumption were considerable, the latter preceded the former by twenty-four hours.

Cases 2 and 3 have been described in the previous section.

Case 4, Table IV. The graphic record of this patient's metabolism indicated parallel fluctuations in the urinary nitrogen and oxygen consumption, but these were dissociated in time, the nitrogen output preceding by 24-48 hours the oxygen intake.

Omitting Case 5 as being unsatisfactory from the point of view of correlation owing to either the shortness of the experimental period or to complicating phenomena such as anuria, &c., the remaining data concerning the members of this group may be summarized as follows:

*Relationship of fluctuations in curves of urinary nitrogen excretion
and basal oxygen consumption*

Case 1, parallel but O₂ preceding N by 24-36 hours.

- „ 2, parallel and coincident in time.
- „ 3, parallel and coincident in time.
- „ 4, parallel but N preceding O₂ by 24-48 hours.
- „ 6, parallel and coincident in time.
- „ 7, not parallel, O₂ preceding N by 48 hours.

It would appear that these curves do run parallel and that, while the fluctuations generally coincide in time, the rise in nitrogen output may precede or succeed the increased oxygen intake.

The average increase in basal metabolism corresponding to these increments in oxygen consumption would be approximately 20-25 per cent. The temperature elevation varied from 97-101° F., corresponding to 36.11°-38.33° C. If we assume the average maximum temperature in these experiments to be 2° C., then the increased basal metabolism found is in agreement with Van't Hoff's Law. Du Bois (1927) has plotted the increase in metabolic rate against the body temperature and found the average coefficient in all fevers to be 2.3.

Rubner's theory (1881) of the secondary dynamic action of ingested protein, provided it is not being stored, has received much light from the experiments of Rapport (1926-27) and his co-worker Beard on the effect of ingested amino-acids. If ingested protein can produce some secondary action on the level of metabolism in virtue of its amino-acids, it may be that the products of proteolysis, which result from injury, can produce a similar secondary effect.

Effect of injury on the urinary volume. It will be noted that in Case 1 there was a retention of water for the first three days of the period of observation and that later there was a compensatory increase. In Case 2 there was a retention of water for the first two days, and following the maximum output of nitrogen there also resulted a compensatory output in urinary volume. It is of interest that on the day preceding the first observable rise in temperature, due to the pulmonary condition which later complicated the experiment, there was again a reduction in urinary volume. In Case 3 there was evidence of a low urinary volume for the first five days following the accident. After the maximum nitrogen output had been observed the urinary volume rose slightly. The evidence in Case 4 was not so definite, but if we rule out the first observation, as being possibly due to a certain degree of anuria during the previous twenty-four hours resulting in a higher value during the following day, then there is some evidence here also of a low urinary output followed by a compensatory increase after the maximum output of nitrogen had appeared. In Case 5 there is evidence not only of the early retention of water in cases of injury, but also of anuria. The remaining two cases do not provide satisfactory data on this question. In case 6 there was a very low output of urine in relation to the intake throughout the period; on the other hand, in Case 7 a low volume was apparent for one day only and was possibly due in part to a diminished intake.

Conclusion

An attempt will be made to narrate in chronological order the development of the phases of the disturbed metabolism which results from injury. The description will thus include the writer's previous observations.

Almost immediately following the receipt of a serious injury there occur in varying degree, but in probably all cases the phenomena of 'wound

shock'. There is often a marked immediate effect, allied to syncope, but this may be delayed by the injured person's unawareness of his injury, as in the intensity of battle. Later, however, the reaction sets in and is in nature providential, as it may lessen bleeding if present. Following on this primary or initial stage of shock or syncope, the area of injury generally suffers further damage through continual movement and the patient's condition is rendered worse through further haemorrhage, exposure to cold, and anxiety. These circumstances aggravate the condition and with very varying intensity there develops a more serious type of shock in that it is more prolonged—secondary wound shock. This generally persists as long as the injured person is subjected to these noxious stimuli. The intensity of these phenomena vary amazingly in different individuals, even when wounds of apparently the same severity have been inflicted.

Urinary excretion. During the stage of depressed vitality or subnormality, there may be relative or absolute anuria occasionally lasting for twenty-four hours. With a return to more normal conditions there is still a diminished urinary volume lasting for another day or two; thereafter the output slowly rises, often irregularly, to a volume practically double the amount passed during the early days. This maximum volume is not generally attained until about two days after the maximum excretion of nitrogen has appeared. The earliest specimens of urine available indicate relatively normal amounts of nitrogen, sulphur, and phosphorus, but these values soon rise, rapidly reaching in the case of nitrogen a value, sometimes two to three times the intake. The maximum daily loss may even exceed 23 grm. nitrogen. This maximum excretion of nitrogen was reached between the fourth and eighth days following the injury in cases suffering from bony and non-bony accidental injury. In the group of post-operative cases this peak value was reached earlier, generally the second to fourth day. The maximum output of sulphur coincided in time with, or occurred on, the day following that of nitrogen. A study of the S:N ratios of the total excess outputs indicates that the substance being catabolized was rich in sulphur, having a ratio of 1:13–1:14. This value is somewhat higher than the generally accepted value for muscle of 1:14–1:15. The reason for this may lie in the fact that the material in muscle being catabolized has not a S:N ratio the same as that of the total tissue, or that the sulphur moiety even over a period of ten to twelve days is still being catabolized more rapidly than the nitrogen moiety. The curves of the urinary excretion of phosphorus, like sulphur, held a course parallel to the output of nitrogen. The peak value sometimes coincided in time with that of nitrogen but sometimes lagged two days behind. The P_2O_5 :N ratio, 1:6.2 indicated that muscle and also probably bone were being catabolized. It was found that in general the maximum daily loss of nitrogen was proportional to the total loss whether estimated over five or over ten days. The total loss during ten days reached as high a figure as 137 grm. nitrogen. In this particular case the reduction in the nitrogen content of the body amounted to 7.7 per cent.

An attempt to correlate the extent of the nitrogen loss with the degree of tissue damage indicated that while there were certain grounds for considering that they were related, evidence was also found that an injury such as the dislocation of an ankle might produce as great a disturbance of metabolism as the splintering of both bones of a leg. It may be that future work will indicate that our conception of the degree of severity of an injury is at fault.

This metabolic disturbance was found to be independent of the use of anaesthetics in the manipulation of injured limbs. It was found that a double osteotomy performed on the femora of a boy, aged 16 years, produced a very less marked disturbance of metabolism than occurred in a boy of the same age who had both bones of one leg broken in a motor-cycle smash. The extraordinary difference in the reaction probably lies, not in the influence of the anaesthetic, but in the adequate splinting and warmth which was applied to the former patient immediately following the operation.

Any factor which tends to set up an arthritis also leads to a rapid wasting of the muscles of the corresponding joint. Therein probably lies the explanation of certain of the effects which follow such simple operations as the incisions of knee joints. The rapid wasting may not occur till some time after the operation. The arthritis is most probably due to the presence of blood in the joint cavities.

Body temperature and oxygen consumption. Observations on the body temperature have indicated that it becomes subnormal during shock (Quénu, Duval, and Mocquot, *Report to Sixth International Congress of Surgery*, loc. cit., Cope, 1929). Aub (1920) has found that severe shock in animals produces a diminution in heat production. Following this phase of depressed vitality occurs generally a period of increased body temperature and heat production. In the present series of experiments this was the phase more particularly studied, although certain cases were analysed within the first twenty-four hours following their injury and also certain cases were examined before and after operation. These experiments have shown that there is generally, though not always, and, therefore, not necessarily, a rise in body temperature resulting from injury. The general trend of the curve is parallel to that of the urinary excretion of nitrogen but precedes it in time. With few exceptions did the rise of temperature exceed 2°C. The pulse-rate tended sometimes to lag behind the temperature, but in other experiments there was an almost perfect correlation. In certain cases with pronounced alterations in the urinary products little or no change in either pulse-rate or temperature was detected. These observations are in agreement with those of Malcolm (1893) who noted that there may be evidence of increased nitrogen metabolism following a major operation yet the temperature remains at a low level.

The basal consumption of oxygen in these experiments was found generally to rise parallel to the increased excretion of nitrogen. The fluctuations

generally coincided in time, but might precede or succeed those of nitrogen by twenty-four to forty-eight hours. The average maximum increase was in the neighbourhood of 20-25 per cent., which is in keeping with Van't Hoff's Law when correlated with the temperature rise.

Following the attainment of these maximum values, all these metabolic increments declined, in particular the body temperature and pulse-rate. The oxygen consumption was not followed for a sufficiently long period to decide what its ultimate level might be. There was evidence that even after six weeks there might still be a definite loss of nitrogen and phosphorus (sulphur not determined).

A comparison of the effects of tissue injury with the general effects of the substance histamine, when introduced into the circulation in comparatively large doses, and with the local phenomena resulting from injury which Lewis (1927) has ascribed to the liberation of H-substance, suggests that these phenomena be considered similar in kind. The depressed vitality, the low blood-pressure, the deficient circulating fluid, the diminished oxygenation, and the reduced body temperature which in varying degree result from injury are paralleled by an almost identical train of symptoms when histamine is injected into the dog, monkey, and man. There is ample evidence that products from damaged tissue play a part in wound shock (Quénu, 1918; Bayliss and Cannon, 1919, &c.).

The tendency for stagnation of the circulation with coincident transudation, while it may partly explain the initial anuria, yet does not explain the increased catabolism which has been observed, unless it be postulated that some unknown toxic product has had such an inimical effect on the cells of the body that they are partially rendered unfit and are catabolized. It may be, on the other hand, that the locally injured tissues are being catabolized to give place to new structures. However, the loss of 7.7 per cent. of the body's content of nitrogen is too great an amount to come from the local area of damaged cells alone. It appears, then, to be of some more general origin, and is probably a rapid catabolism of the body's substance in response to the exigencies of repair and maintenance.

Summary

1. During the initial phase of depressed vitality or subnormality which generally resulted from the moderate or serious physical injuries to the limbs here described, there occurred within the first twenty-four hours a period of relative or absolute anuria of varying duration.

2. Following on the early period of diminished urinary secretion the volume of urine and the output of nitrogen rose considerably, reaching in the latter case a maximum daily loss during the fourth to eighth days which might even exceed 23 gm. The maximum secretion of urine generally occurred two days after the maximum output of nitrogen. The reduction in the nitrogen content of the organism might exceed 7 per cent. in the first ten to twelve days following a serious injury.

3. There appeared to be some relationship between the extent of the injury and the degree of reaction, but there was great variation in individual cases.

4. During the initial period of depressed function the patient's heat production and body temperature were diminished, but during the subsequent phase of enhanced vitality there was an increase in heat production and body temperature. With few exceptions did the rise in temperature exceed 2°C . The increase in the 'basal' consumption of oxygen was generally 20–25 per cent. This increase in heat production as estimated by the change in oxygen consumption is in agreement with Van't Hoff's Law. Coincident generally with the rise in temperature was a rise in pulse-rate, the rate of increment being ten beats per 1°F .

5. The curves of the urinary excretion of nitrogen and the basal consumption of oxygen were generally parallel; the oxygen fluctuations, while generally coinciding in time, might yet precede or succeed the corresponding changes in nitrogen by 24–48 hours.

In conclusion I wish to thank Professor E. P. Cathcart for his continued interest in this work. My thanks are also due to Professor P. Paterson, and to Messrs. Patrick, Macewen, McIntyre, Duff, and Taylor, for supplying me with suitable patients. Further, I wish to thank my nursing staff for their active co-operation in these experiments.

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SPONTANEOUS OVERBREATHING TETANY¹

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HYPERVENTILATION tetany in man was produced and substantiated experimentally (1, 2, 3, 4, 5, 6, 7) before it was recognized as a clinical syndrome (8, 9, 10, 11). Since 1922 the literature on the subject has become extensive. Experimentally, tetany has usually been observed after ten to thirty minutes' overbreathing, and clinically after equally prolonged and obvious hyperventilation (41). Such overbreathing washes so much CO₂ out of the lungs that a measurable change of the reaction of the body takes place towards the alkaline side. The pH of the blood rises and a very alkaline urine is secreted in compensation. Clinically, the latter should usually be of diagnostic value, if, as so often happens, the patient is not seen till the attack is over. The test is of less value if the bladder was full before the attack began.

The two cases now to be described show how short a period of overbreathing may suffice in certain subjects to induce an attack of tetany, and how difficult diagnosis may be in such cases, as in them chemical changes can hardly be appreciated by existing methods.

Case 1

Female, aged 31, an efficient nursing sister in a responsible position. She takes her duties so seriously that they tend to be a drain on her nervous and bodily strength.

Past history. Appendicular abscess and partial appendicectomy twenty years ago in China; since then there has always been a tendency to abdominal discomfort, which has become gradually worse. The patient has suffered from 'palpitations', especially after food. Movement of the bowels has always been difficult, but the stools have been normal in appearance.

Family history. Some years ago a sister had a finger nail removed under gas anaesthesia, and shortly after was observed in a state of tonic flexion of the arms and fingers, but no definite diagnosis of tetany was made at that time. There is no history of neurosis in the family.

Present attack and investigation. On March 2, 1931, while in the operating theatre, the patient had violent and prolonged palpitations. Soon after, she had tonic spasms of the arms and legs. A tentative diagnosis of tetany was made, and the patient was put to bed. Clinically, her heart and lungs were

¹ Received October 27, 1931.

found to be normal, and it was thought that some adhesions could be felt in the appendicular region. Nothing abnormal was discovered in the nervous system, and Chvostek's sign was not obtained. Her blood calcium was normal (10.1 mg. per 100 c.c.), and also the inorganic phosphate of the blood (3.3 mg. per 100 c.c.). During the next few days in bed the patient had severe palpitations on several occasions, and twice experienced tingling and an incipient stiffness in the fingers. The urine was always acid after these attacks, and the patient was never noticed to be breathing more deeply than usual.

On March 7 the patient was asked to breathe deeply. She was at the moment having mild palpitations. At this time she knew nothing of the connexion between overbreathing and tetany. The patient began to breathe more deeply, but not to the extent of obvious hyperventilation. In half a minute a blotchy erythema appeared on her neck, and she announced that her hands were tingling. In one and a half minutes the patient was in a severe attack of tetany, and Chvostek's sign was obtained. The urine obtained shortly afterwards was amphoteric (pH 7.1 by capillator, B.D.H.), which was not more alkaline than was to be expected two hours after breakfast. The palpitations ceased after the attack. During the attack her arms were flexed at the elbow and wrist; her thumb was adducted, while the first and second fingers were fully extended and spread out; her third and fourth fingers were in a position of slight flexion. Some such departure from the typical 'accoucheur' posture is characteristic of overbreathing tetany.

Further experiments were made on this subject.

1. After samples of venous blood had been taken without stasis the patient was requested to breathe deeply. The overbreathing was again of a very mild character. In one minute her hands were tingling, and the blotchy erythema had again begun to appear; in four minutes the attack was at its height. Blood was then again taken, and analysis subsequently showed that the two samples of blood were almost identical:

	Before.	After.
Blood pH * (by glass electrode)	7.35	7.35
Serum Ca. (Kramer and Tisdall (12))	10.7 mg.	10.7 mg.
	per 100 c.c.	per 100 c.c.
Alkali reserve (Van Slyke (12))	54.0	50.0

* I am indebted to Dr. Hurst, Maudsley Hospital, for this determination and other determinations of the blood pH.

2. The electrical reactions were very kindly investigated by Professor Hartridge and Dr. West at St. Bartholomew's Hospital. A special apparatus devised by Professor Hartridge was employed (42). Their findings were as follows:

Minimum current required to excite contraction in *flexor sublimis digitorum*:

	Left.	Right.
K.C.C.	1.7 milliamps.	0.75-1.4 milliamps.
K.O.C.	1.45 "	4.4 "
A.C.C.	2.35 "	2.1 "
A.O.C.	3.3 "	2.2 "

Dr. West considers that these figures show slight hyperexcitability (a) because K.O.C. on the left is so low (normal, 4.5-10), (b) because A.O.C. = A.C.C., whereas normally A.O.C. is approximately A.C.C. \times 2. On

applying a sphygmomanometer band at 160 mm. Hg. for two to four minutes to the right arm above the elbow, K.O.C. fell to 0.4 milliamps., rose again to 4.7 on removing the armlet, and fell once more to 0.4 on replacing the armlet. No change took place in the electrical thresholds after four minutes' overbreathing which brought on an attack of tetany.

3. Several experienced physicians who had not seen one of these attacks, but with whom this case was discussed, independently suggested that the seizures were entirely hysterical, and that alkalosis and overbreathing played no part in the aetiology. Accordingly a simple apparatus was made with an anaesthetic mask by means of which the subject could be made to breathe either air or a mixture of carbon dioxide and oxygen (4.75 per cent. CO_2 by estimation). The subject was asked to breathe deeply, and at first the CO_2 mixture administered. After six minutes the patient was quite normal, and, unknown to her, air was now substituted for the CO_2 mixture. The rate of ventilation fell off somewhat, but in three and a half minutes tetany was fully established in the right arm and hand, and the left quickly followed. At this point the CO_2 mixture was again administered, and, after a few breaths, the patient's hands fell back completely limp to the bed, and the tetany and experiment terminated.

Course of the disease. The patient had no further attacks after she appreciated how they were produced and that they were under her own control. A laparotomy was performed under gas and oxygen with rebreathing, the mass of adhesions round the caecum freed, and the caecum plicated. The stump of the appendix was also removed. This operation has been entirely successful in removing the abdominal discomfort, and the patient is now back at work and in excellent health.

Case 2

A nurse, aged 21. Except for occasional headaches her previous history and health have been excellent. From March 1 to 28, 1931, she was on night duty, and on the morning of the 28th went to bed soon after coming off duty with a sore throat and headache. In the evening she had to be called three or four times for duty, and was aroused only with difficulty. Finally, she went to her ward without food. She had taken no drugs. She remembers having a very severe headache that evening. During the night she was twice found asleep by a junior nurse. About 3.45 a.m. she remembers going to make some tea, but nothing more. She was found soon after this lying on the floor unconscious. During the night part of her duties had been to write reports and notes on the patients under her charge. Her night report is valuable evidence of her state of mind. The writing is barely legible whereas her normal writing is excellent. The words stray off the lines in all directions, and most of the entries are fragmentary. They show also in places the phenomenon of perseveration, e.g. 'good' is written 'good', and 'Newcombe' (one of the patients) is written 'Newcombecombe'.

On March 29 she recovered consciousness, but had an intense headache and photophobia. Her temperature was normal.

On the 30th a diagnosis of spontaneous subarachnoid haemorrhage was made. A lumbar puncture was performed, but the fluid was found to be normal. On the 31st she was again examined, and her chest and abdomen

found to be normal. Directly after this examination she felt cold and rang for an extra blanket. She was then found in a fit which was diagnosed as tetany. That evening there were slight weakness of the muscles supplied by the seventh cranial nerve on the left side and signs of a cerebellar lesion on the right side, viz. deviation of the outstretched arm, hypotonus, and dysdiadokokinesis. Chvostek's and Trousseau's signs were present.

On April 1 the patient's headache was less severe and an overbreathing test was made. Urine was collected before the test commenced, and venous blood was taken without stasis. After one minute of vigorous overbreathing the patient announced that her hands were tingling, and in another half minute tetany commenced. Soon after, a paroxysm of overbreathing set in, and in three minutes from the start the patient was rigid all over, with arms and legs intensely stiff and with head retracted. The fingers were fully extended and separated, the wrists were flexed, and the elbows partially so. The legs were fully extended at the knees, the ankles were plantar flexed, and the toes fully plantar flexed. Blood was collected immediately without stasis, and urine as soon as possible.

		Before.	After.
Blood.	Alkali reserve (Van Slyke (12))	54 vols. %	47 vols. %
Serum.	Ca (Kramer and Tisdall (12))	10.96 mg.	11.46 mg.
		per 100 c.c.	per 100 c.c.
"	Mg. (Watchorn (13))	2.28	2.34
"	Na. (McCance and Shipp (14))	350	355
"	K. (Kramer and Tisdall (15))	—	23
	Plasma inor. PO ₄ (Briggs (16))	2.4	2.1
	Urine pH (B.D.H. capillator)	5.6	6

The changes in the blood, although slight, are in the same direction as in prolonged breathing experiments (17, 18, 19, 2, 4). The urine shows how slight a change in the pH of the blood can have taken place.

On April 8 a breathing test with a mixture of carbon dioxide and oxygen was made in the way already described and with identical results. On April 9 the patient got up. The cerebellar ataxia was very striking as the patient was unable to prevent herself deflecting to the right even with her eyes open.

Dr. West very kindly investigated the patient's electrical reactions with the following results:

Resting (breathing normally)	Left.	Right.
K.C.C.	2.1 milliamps	2.55 milliamps
K.O.C.	4.5 "	8.0 "
A.C.C.	2.35 "	2.95 "
A.O.C.	4.7 "	9.5 "

These he considers within normal limits. On applying a sphygmomanometer for three minutes to the right arm K.O.C. fell to 3.3. After a pause overbreathing was then undertaken with the bag on the right arm. K.O.C. on the left side fell to 2.5, but there was no change on the right, although tetany developed first on this side.

Course of the disease. The cerebellar signs gradually receded, until by June the patient was normal except for questionable weakness of the muscles supplied by the seventh cranial nerve on the left side. She could walk straight with her eyes shut. She returned to duty on June 26. On August 26 she complained of diplopia and giddiness with a severe headache,

and, when first seen, could not stand upright, falling at once to the right. Obvious nystagmus to the right was present. Her abdominal reflexes were absent, but Babinski's plantar toe reflex was negative. On the 28th the abdominal reflexes had returned and there was no nystagmus, but slight weakness of the muscles supplied by the seventh cranial nerve on the left side and cerebellar signs on the right were noted, viz. past pointing of the right hand, slight hypotonus, deviation outwards of the outstretched hand. An examination of the cerebrospinal fluid, including Lange's curve, revealed nothing abnormal. A spontaneous attack of tetany followed the lumbar puncture, and on the following evening, while engaged in casual conversation with her room-mate, she suddenly fell silent and had a severe attack of tetany. All objective signs have now disappeared, and the patient appears physically sound. It must be admitted that no certain diagnosis has been reached.

Discussion

1. *Diagnosis.* Both these cases of proved hyperventilation tetany have been induced by so little overbreathing that there have been practically no estimable chemical changes either in blood or urine; and, in Case 1, even the overventilation was barely noticeable. Are many of the cases of so-called sporadic tetany of this type? The only certain diagnostic procedure in the presence of a doubtful case is to make the patient overbreathe. There is no contra-indication to this. It is harmless. It shows the patient how the attacks are brought on, and gives him confidence and assurance that he can prevent any recurrence.

2. *Time of onset.* Experimentally, tetany usually appears after fifteen to forty-five minutes' forced breathing. Signs of tetany have only once been recorded experimentally after so short a time as two minutes (20). Rosett (21), whose paper is based on over 1,000 overbreathing experiments, gives two minutes as the minimum time, and states that he has only found this in the presence of abnormalities of the central nervous system. Such abnormalities were undoubtedly present in Case 2, and may have influenced her susceptibility to overbreathing, but they were absent from Case 1. Rosett states that the presence of pain makes it easier to induce tetany, and this may have been a factor in Case 1, but was probably relatively unimportant, as tetany was induced experimentally with great ease in the absence of all pain.

3. *Aetiology.* Assuming that the change of the body's reaction to the alkaline side is the cause of tetany associated with overbreathing, it is quite evident that certain persons must be peculiarly susceptible to such changes, just as certain persons have an idiosyncrasy for certain drugs. Why they should be so, if their blood calcium is normal (Snell and Habein (22)), we have at present no certain knowledge. It is not even definitely known what part of the nervous system responds to the increase of OH ions. Behrendt

and Freudenberg (23), Behrendt and Klonk (24), and György (25) think that the action is entirely peripheral, but this is not the opinion of most of those who have studied the problem. Thus Schäffer (26), Flick and Hansen (27), have shown that the muscular spasms give an electrical myogram identical with that of a voluntary contraction, indicating participation of the central nervous system, and through the kindness and co-operation of Dr. Golla we have been able to confirm this in Case 2. Further, Flick and Hansen (27), and Freudenberg and Låwen (28), have shown that tetanic spasms are abolished by cutting the motor nerves or by the application of novocaine to the trunks. Moreover, although Behrendt and Freudenberg (23) stated that tetany did not develop in an arm through which blood was prevented from flowing by a tight band, spasms developed normally in both Cases 1 and 2 even when a sphygmomanometer was kept on the upper arm at 160 mm. Hg. throughout overbreathing. This must have effectually prevented the access of OH ions to the peripheral endings, and indeed have increased the H ions there, and suggests that the OH ions must have been acting on the central nervous system. Tetanic spasms have been reported in connexion with various lesions of the central nervous system (29, 30, 31, 32). Duzár and Fritz (33) have stated that decapitation prevents the onset of hyperventilation tetany in cats. Rosett (21) believes the tetanic posture and spasms to be cortical in origin, and his evidence is very convincing. He states among other things that right-handed persons first get the spasms in the right hand, and vice versa. This was certainly true of both Cases 1 and 2.

Trousseau's sign is generally regarded as reflex in origin (26), and it clearly must be so when the spasm develops on the opposite arm (30). It is hard to explain why, if it is a simple reflex, the excitability of the peripheral nerves of Cases 1 and 2 were increased, as measured by the fall in K.O.C., when the blood-flow through the arm was prevented by the tight band. This may be some totally different phenomenon.

4. *The action of adrenalin.* A number of authors have stressed the importance of adrenalin in the production of overbreathing tetany (34, 35, 36, 37). All these authors agree that adrenalin increased all the effects of overbreathing, and Duzár and Hensch (37) state that children can seldom induce tetany by overbreathing unless adrenalin be injected. Golant-Ratner (34) investigated a series of cases with 'asymmetrical sympathetic tone', and found the effects of overbreathing invariably more definite on the hypertonic side. Redlich (30) has reported a clinical case of unilateral tetany greatly accentuated by adrenalin. On April 11, therefore, Case 2 was given 0.2 c.c. of saline intravenously. Respirations, pulse, and appearance remained unchanged. Ten minutes later 0.1 mg. adrenalin hydrochloride was administered intravenously. Respirations rose instantly from twenty-one to forty-four per minute, and became very deep and unrestrained. An attack of tetany was only avoided with the greatest difficulty. A few days later a quantitative experiment was made. The patient was placed on the couch beside the Sanborn spirometer, and 0.1 mg. adrenalin hydrochloride was

injected subcutaneously. Spontaneous hyperventilation commenced in about thirty seconds, and measurement of the volume of gases expired then began. The subject expired *85 litres* in two minutes, five seconds, and by then tetany was fully established. On the following day, with the intention of paralysing the sympathetic nervous system, the patient received 0.5 mg. ergotamine tartrate subcutaneously. As her pulse-rate did not fall more than five beats per minute and she felt nothing abnormal, a further 0.5 mg. was injected in half an hour to ensure that she was under the full action of the drug, and soon after the patient was connected to the gasometer as on the previous day. She felt no tendency to overbreathe, but when told to do so expired *87 litres* in *two minutes*, at which time the degree of tetany was indistinguishable from that of the day before. These experiments, make it quite clear that the action of adrenalin on this woman is to stimulate respiration, possibly by a direct action on the respiratory centre or possibly through the cortex, but that it has no other action in accelerating hyperventilation tetany. An effect of adrenalin on respiration similar to this, but very much milder, was noted by Bornstein (38), and Lyman, Nicholls, and McCann (39). It is possible that the accelerating influence of adrenalin on hyperventilation tetany studied by Duzár (37) and others may have been due to this effect on respiration. Brehme and Popoviciu (35) consider respiratory stimulation the chief action of adrenalin in promoting tetany.

5. *The effect of overbreathing on the electrocardiogram.* Kronenberger and Ruffin (40) reported in 1929 that, during overbreathing tetany, alterations took place in the normal electrocardiogram. This was accordingly studied in both cases, with the co-operation of Dr. East. In order to avoid the movements of the limbs direct leads to the chest were used, the contacts being applied in the positions corresponding to the usual leads. In Case 1 no change was observed in any of the deflexions during tetany. The only alteration was tachycardia. In Case 2 the following observations were made:

- (1) Before overbreathing commenced.

Rate 90.

Height of *T*-waves in millimetres:

$$T1 = +4.0, \quad T2 = +5.0, \quad T3 = +1.0.$$

- (2) Three minutes after overbreathing began; tetany very violent.

Rate 150.

Height of *T*-waves in millimetres:

$$T1 = +0.5, \quad T2 = +2.5, \quad T3 = +2.$$

There were considerable respiratory variations in *R1*.

- (3) Five minutes after the tetany had subsided.

Rate 120.

Height of *T*-waves in millimetres:

$$T1 = +1.0, \quad T2 = +2.0, \quad T3 = +1.0.$$

As a control it was hoped to see whether acceleration due to exercise would affect the *T*-waves. The heart-rate, however, fell so rapidly after

exercise that the resting-rate was regained before the direct leads could be applied.

The usual immersion leads were therefore employed for this experiment.

(1) At rest.

Rate 90.

Height of *T*-waves in millimetres:

$$T1 = +1.0, \quad T2 = +2.0, \quad T3 = +1.0.$$

(2) At once after exercise (running up and down stairs).

Rate 156.

Height of *T*-waves in millimetres:

$$T1 = +1.0, \quad T2 = +2.0, \quad T3 = +1.0.$$

In this case, therefore, there was a diminution of both *T*1 and *T*2 during the tachycardia associated with tetany, but not with the tachycardia due to exercise.

These observations are merely recorded as facts. No explanation for them can be offered at present. A reduction in the height of the *T*-waves of leads 1 and 2 were the main changes recorded by Kronenberger and Ruffin, and the interest attached to the present study is that it not only confirms the previous findings, but shows that heart changes may be very quickly induced in a susceptible person. In all probability, therefore, they are a genuine part of the tetanic syndrome, and not merely the result of prolonged overbreathing.

Summary

1. Certain persons are peculiarly susceptible to the changes of reaction brought about by overbreathing. Tetany may develop in these persons with scarcely noticeable overbreathing and before any definite chemical change can be detected. Investigations upon two such persons are described.

2. Many of the cases of so-called sporadic tetany in adults may be of this type. Diagnosis is easily confirmed by making the patient overbreathe. This procedure is harmless, and demonstrates at once to the subject the cause of the attacks and how to avoid them.

3. Experiments with adrenalin in one case suggest that this drug has no direct action in producing tetany, but that it may do so by stimulating hyperventilation.

4. Associated with the tetany one case showed a reduction of the *T*-waves in the first and second leads of the electrocardiogram.

I am indebted to Dr. Douglas Firth for permission to investigate and publish these cases. I wish also to thank Professor Hartridge, Drs. West, Golla, East, and Lawrence, for co-operation in different stages of the investigation, and Dr. Critchley for his advice and suggestions.

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THE MOBILITY OF THE ABDOMINAL VISCERA¹

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With Plates 9-13

Introduction

THE purpose of this paper is to advance the thesis that mobility and adaptability to changing circumstances are the essential characteristics of the abdominal viscera, and that fixation or a constant relation between the organs, either to each other or to the abdominal wall, is foreign to Nature's design.

It is surprising that the positions taken up by the organs after death provide such a constant anatomical pattern, for, normally, there are no fixed points and no fixed organs in the abdomen. Moreover, there is far less relative fixity of one organ in regard to another than our anatomical teaching would ever allow us to accept as a possibility. In fact, the conception of the living anatomy is one of mobility, with an entire absence of fixed points.

The bearing of the observed facts on abdominal surgery seems even yet inadequately appreciated, and I hope that this small study will do something to prick the last bubble of fixation and similar operations. The one thing to be avoided is the production of fixed points, for these must interfere with and hamper nature's mechanism.

It is highly artificial to attempt the separation of form from function, anatomy from physiology, but for convenience of text-book descriptions it is usual in one section to describe the position of organs and in another to give an account of their movements and function. In adopting this plan here and dealing only with the anatomical side, I am nevertheless well aware that the two subjects should not be thus divided.

Historical Survey

The literature on the subject of displacement and mobility of the abdominal viscera is profuse, but the salient points are here briefly summarized.

The early anatomists regarded the abdominal viscera as having definitely fixed forms, positions, and relationships, and any departure therefrom was considered abnormal. Thus, Franciscus de Pedemontium (44) described a

¹ Received September 3, 1931.

dislocated kidney in 1589, and Antonius de Haen (26) published in 1747 several plates showing such abnormalities as an undescended caecum and a transverse colon looping down below the umbilicus. In 1761, Morgagni (42) described twenty autopsies in which he found the stomach and colon abnormally low, and stated that he had observed the same in many other cases. He believed that this disposition of the viscera was far more common than was usually supposed, and suggested that these abnormalities might be congenital in origin.

In 1825, Baillie (5) described movable kidney in a healthy woman, and in the following year Aberle (1) published four autopsies where the kidney, palpable during life, was found unduly mobile *post mortem*. Meckel (37), writing in 1812, was the first to observe that the stomach frequently, and especially in women, occupied a vertical position instead of the classical horizontal one.

As Bedingfield remarks (13), there was utter confusion for many years on the subject of gastropptosis and allied conditions, and this was not clarified by the French writers, who, using the stomach-tube, assumed that a low position of the stomach indicated atony or dilatation.

The name of Glénard is closely associated with the condition of ptosis and abdominal looseness by reason of a series of papers which he published from 1886 to 1899, the main contribution being *Les ptoses viscérales*, published in Paris in 1899 (24). Glénard (23) was the first to connect the condition of prolapse of the abdominal viscera with certain local and general symptoms, and the symptom complex has since borne the name of Glénard's disease. He regarded the low position of the colon as an important feature, and he used the terms visceroptosis and enteroptosis synonymously. At first Glénard gave mechanical explanations for the descent of the viscera, but later on shifted his ground and held that the abdominal wall was not the chief factor. He then suggested that the cause of enteroptosis was a reduction of intestinal volume dependent on perverted liver function, leading to deficient gas content in the bowel.

Invalidism, associated with flabbiness of the abdominal wall and lack of resistance in the epigastrium, has been dealt with by many writers, particularly, in this country, by Treves (49) and Allbutt (2) in his lectures on visceral neuroses (London, 1884). A deluge of literature, perhaps as many as a thousand communications, appeared in the early years of the twentieth century up to 1912. Bedingfield (13) has given a very complete and critical survey of the history and of the literature.

In the early X-ray observations many views were expressed as to the conditions present in gastropptosis. Leven and Barret (33) maintained that when the stomach was dropped the cardiac end was drawn away from the diaphragm. Schlesinger (46) also thought that the lengthening of the stomach drew down the cardia, but Bécélère and Meriel (12) demonstrated that the cardia did not leave its position under the dome of the diaphragm. In 1908, Cerné and Delaforge (18) defined gastropptosis as a deformity in

which the 'grand cul de sac de l'estomac' disappeared coincident with some drop of the lower border. Groedel (25 A), in 1910, held that the low position of the pylorus was the most important point in the diagnosis of gastropptosis, while Holzkecht (28), in 1906, considered that gastropptosis was present when the pylorus was not the lowest part of the stomach, and Kaestle (32), in 1913, regarded a high pylorus with a lower greater curvature as the criterion. Hurst (29), in 1915, defined gastropptosis thus: 'When the stomach is not only abnormally low in the erect position, but the greater curvature reaches below the umbilicus in the horizontal position.' He also laid it down that there are two general forms of the normal, the cow's horn and the fish-hook or J-shaped stomach.

In order to reach a clear conception of the normal stomach, Mills (38) and Ansell (4), in America, carried out extensive observations on students and others, but apparently worked on a preconceived idea that each individual could be fitted into certain types: hypersthenic, sthenic, hyposthenic, and asthenic, and that for each type there was a more or less constant stomach form. From observations on 2,500 patients with gastric disturbances, Mills (38) drew the important conclusion that there was no causal relationship between the form and position of the stomach and the digestive symptoms. He also noted that the passage of the food through the tract did not appear to be influenced by the position of the viscera and the tone of the gut.

Barclay (10), in 1922, says that, 'generally speaking, gastropptosis is normal in the long thin subject, the small hypertonic and well-contracted stomach is usually found in the short stout type of man'. He held that gastropptosis was not apparently, *per se*, of significance, but when the duodenum remained in its normal high position, a drag was produced on the attachments which might give rise to symptoms suggestive of duodenal trouble, because the lesser curvature was not lengthened, and consequently the duodenum was not dragged upon, but, on the other hand, the pylorus was very high compared with the lowest part of the stomach, and there was mechanical disability which interfered with the emptying, quite apart from any suggestion of obstruction. The tonic action stabilized the stomach, held it in posture, and counteracted the diaphragmatic movement and gravitational effects.

The most extensive study of the normal stomach is that of Moody (1923, 1925), who, with Nuys and Chamberlain (41), examined 600 healthy American students in the upright posture. Later (41 A), they studied their subjects both in the vertical and recumbent position, finding greater variation in the female than in the male. The pylorus lay anywhere from the upper border of the first lumbar vertebra to a point 5 cm. below the interiliac line. This accurate and painstaking study was continued by Moody in London (40) on 100 English students with the same results. Moody concluded that the stomach, caecum, and colon were able to function normally irrespective of their positions. Among other workers who have come to the same conclusions are Faber (21), and Campbell and Conybeare (14).

On the clinical side, Conran (19) showed that the low stomach was quite compatible with perfect health, and that symptoms cannot be associated with any particular gastric form.

Barclay (6 and 10) has pointed out that tone is independent of the position of the stomach and of its peristaltic activity. He regards atony as defective physiological action rather than a pathological condition. Hurst (31), who also held this view, concluded that the terms hypertonic and atonic were misleading, since manometer experiments showed no change in the intra-gastric pressures as compared with the normal. He showed that the tone of the muscle adapts itself automatically to the volume of the contents, and that the pressure remains constant. Experiments also gave the same result in both the hypertonic and the dropped stomach, and he considered that the only satisfactory explanation was to accept these different forms as anatomic variations in type.

Chamberlain (41) observed that an athlete, by training the abdominal muscles to an abnormal degree, produced no appreciable alteration in the disposition of the viscera, and Mackeith, Spurrell, Warner, and Westlake (36) in 1922 reported an important case of congenital deficiency of the anterior wall of the abdomen in which they found the stomach normal in tone and occupying a position, if anything, slightly higher than normal in spite of this defect, thus proving that the position of the stomach is not necessarily dependent on the support of the abdominal wall.

Many theories have been advanced as to how the organs are maintained in position in the abdomen, and why in some cases 'displacements' apparently give rise to symptoms. Keith (34) in 1903 held that the diaphragm was the chief factor in maintaining the position of the viscera, being so delicately poised that any alteration had a marked effect on the abdominal contents. Later (35), he came to regard the transversalis muscle as an important factor in regulating the piston action of the diaphragm and thus holding the viscera in position. He held that the function of the mesentery was to limit movement (35) and not to act as a support, an idea which fits in with Alvarez's (3) contention that the viscera 'float' in the abdomen. Although most writers, however, regard the abdominal wall as of the greatest importance, Vietor (50) argued that the fundamental cause of visceroptosis was a failure of normal development which was usually associated with a retracted lower thorax. This resulted in an alteration of the size and shape of the abdominal cavity, and was accompanied by defective fixation of the viscera.

The possibility of kinking of the intestine as a cause of symptoms was very prominent for a time. It was suggested that these kinks were often due to the low position of the viscera, but Hurst (29), Barclay (8), Mixter (39), Schwarz (47), Carman (15), and many others were unanimous in stating that, apart from adhesions, they had never found such a condition obstructing the onward passage of the food. The mobile caecum and proximal colon have been regarded as the cause of symptoms by Hausmann (27), Waugh (51),

Morley (43), Carslaw (16), and others, but Flint (22) and Carson (17) were sceptical of this explanation.

Factors Influencing Form and Position

There are many factors that may influence the appearance of living organs as they fulfil their functions. The effect of mental influences on the stomach, as instanced by fear, nausea, &c., has already been pointed out by Barclay (7 A). Todd (48) has carried these studies farther, and has also recorded the influence of various types of food. Such factors cannot be overlooked, although they are not so readily studied as are mechanical influences.

The main factors responsible for change in shape are: (1) The posture of the subject. (The influence of gravitation.) (2) The tonic action of the gastric muscle. (3) The movements of the diaphragm. (4) The distension of the organ by the bulk of the food. (5) The weight of the food. (To a small extent only.) (6) Pressure from other organs.

Of these, I am only dealing in this paper with the effects of gravitation and respiration. The effect of the pressure of other organs will only be mentioned incidentally. Weight and bulk of food are more or less indivisible, and their effect is closely bound up with that of gravity and tone. It is obvious that the movements of the abdominal organs and the modifications of their shape must at all times be due to a resultant of the forces at work.

The detailed examination concerns only three normal subjects who consented to undergo the tedious X-ray and photographic experiments. But behind these cases is a background of observation on many thousands of patients during twenty-five years of study. This makes all the difference in the use to which such limited experimental material can be put.

The three subjects studied were 'normals', selected merely because they were available. The stomach pattern that would be revealed was not known. The young woman, aged 27 (A, Plates 9-13, Figs. 10-18), is a healthy well-built subject of good physique. The man, aged 20 (B, Plates 9-13, Figs. 20-29), is an athletic student. He happens to have six lumbar vertebrae, the umbilicus corresponding to the fourth to fifth intervertebral disk as in the other subjects. The third subject, a woman of 55 (C, Plates 9-13, Figs. 30-38), is an active, healthy, but thin woman.

In the numbering of the figures in these plates the same unit (e.g. 12, 22, 32) has been applied to a corresponding posture in the three subjects.

Technique

Plates 9, 10, 11, 12, and 13, Figs. 10-38. *Technique of the composite photographs.* My first essay in these investigations was by fluoroscopic methods, but the records thus obtained were not satisfactory. I therefore attempted to produce a composite picture by superimposing radiographs of the organs

on to photographs of the subject. The scheme was, first, to obtain photographs; then, secondly, radiographs of the vertebral column; and, thirdly, radiographs of the stomach and intestines. If correctly superimposed, these three ought to give a reasonably accurate representation of the relationships of the organs both to the surface of the body and to vertebral levels. Experience showed that the inclusion of the whole of the vertebral column introduced too many difficulties and this was abandoned, and only so much of the spine as showed in the X-ray films of the organs was included in the composite pictures. For the benefit of any one who wishes to repeat this technique, I would point out that in this work we are taking radiographs of large areas that include the organs, and are not centring on a definite point. The central beam is in the middle of the radiograph, while the surface landmarks, for repositioning on the photographs of the patient, are usually some distance from the centre, and therefore correspondingly liable to distortion. The tracings of the radiographs of the viscera can, therefore, only be placed in position with a general degree of accuracy. The vertebral level corresponding either to the umbilicus or to a surface mark representing the diaphragm level was generally used, and some allowance made for the distortion. I realize that such pictures are not accurate, and that they cannot, even with every precaution, be made accurate, yet I maintain that they are sufficient to demonstrate the essential fluidity of the living anatomy as seen by the radiologist.

Skin markings change their position according to posture. For instance, in one subject the umbilicus corresponded to the fourth to fifth lumbar vertebrae in the upright position, while in the supine position it moved up to about the third to fourth lumbar vertebrae. This disparity was much increased by flexing the legs. Nor are skin markings over the spine much more reliable. In two cases where I tried this, the mark was a whole vertebra higher with the subject lying on the back. There may even be a considerable displacement of the skin over the chest. I noted in a thin subject that my markings were displaced a half to three-quarters of an inch when the subject lay down.

In deep inspiration and expiration any point of the anterior abdominal wall and the chest rises and falls considerably in relation to the vertebrae, so that, if surface markings are given, the respiratory conditions in which these are made must be stated. The photographs of subject *A* (Plates 9-13, Figs. 10-18) were taken in the various phases of respiration, and it will be noted that between this subject and the others who were photographed in the position of rest only, there is very little apparent difference, certainly not enough to catch the eye if it was not pointed out. For the figure of the subject lying on the back, I had to use the photograph of the standing subject, as I had no facilities for placing a camera sufficiently high above the couch.

When all the conditions of an examination are apparently identical, it does not follow that in subsequent observations organs will always occupy the same position, even relatively to each other. For instance, in subject *B*,

I carried out two sets of investigations on the colon (Plate 13, Figs. 28 and 29). It will be noted that the transverse colon was about two inches lower on the second occasion—possibly (or probably) because the subject was nervous about the proximity of a *viva voce* examination. The difference in the position of the splenic flexure in these two pictures is also noteworthy, but I cannot explain it. It certainly does not seem to be connected with the weight of the food.

The Normal Stomach and Variations

Plate 9, Figs. 10, 20, and 30. *Erect position; mid-phase of respiration; at rest.* The *cardiac orifice* is the one relatively fixed point in the abdomen, but, owing to the attachment of the oesophagus to the diaphragm, is naturally subject to the movement of that muscle. The orifice is situated about the level of the twelfth dorsal vertebra and to the left side of it. Apart from exertion, it moves about half an inch between inspiration and expiration, but on deep respiration it appears to move just as much as the maximum excursion of the diaphragm, perhaps three inches. It is not, however, at all easy to verify this, as the opaque food usually slips through before the observation is completed.

The position of the *pylorus* is given in the old text-books as being to the left of the first lumbar vertebra. In practice its position may vary within wide limits, not only according to the type of the stomach, but with the posture of the subject. It is capable of a wide range of movement. On an average I would place the position of the pylorus in the ordinary J-type of stomach in the upright position as slightly to the left side of the third to fourth lumbar vertebrae. When the patient lies down, it moves upwards to somewhere near the first to second lumbar vertebrae. In the small hypertonic stomach, it may even be as high as the lower border of the twelfth dorsal vertebra, while in the long stomach (as in Plate 9, Fig. 30) it lies at the right side of the fourth to fifth lumbar vertebrae. Figs. 1, 2, and 3 in the text, indicate the mobility of the pylorus and the positions in which it was found under varied conditions of respiration and posture. These show how mobile is this part of the stomach. It appears to have a range of possible movement, perhaps five inches in diameter in these cases, and I do not think this is anything unusual.

When we compare the mobility of the pylorus in these three cases, we are at once struck by the comparatively limited range in the last subject, *C* (Fig. 3), the elderly woman. It is considerably less than in either the young man or the young woman. This is probably because the long 'dropped' stomach is supported to some extent on the pelvic contents. By manipulation I have sometimes elicited a remarkable range of movement of the pylorus in cases of this type, but in the present investigation only posturing is considered. It is, however, rather striking that the range of movement of the pylorus appears to be greatest in the young athletic man.

The deduction from these observations is that the pylorus is free to move within a radius of some inches, and that this wide range of movement is found to be just as great in perfectly healthy, young, athletic subjects as in subject *C*, who has a relatively lax abdomen and a long stomach. The range of movement noted in the healthy young subjects is very striking. Had such movement been discovered in a patient who had abdominal symptoms, it would have been difficult to resist associating it as the cause. We must, however, accept such free mobility as being quite normal.

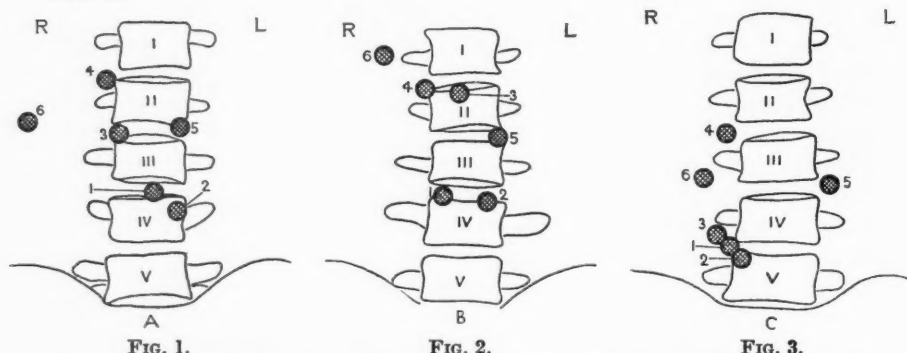


FIG. 1.

FIG. 2.

FIG. 3.

The position of the pylorus in various postures and also in the extremes of respiration.

- | | |
|---------------------------------|------------------------------|
| (1) Standing at rest. | (4) Lying on the back. |
| (2) Standing. Full inspiration. | (5) Lying on the left side. |
| (3) Standing. Full expiration. | (6) Lying on the right side. |

FIG. 1. Healthy woman, aged 27. (Subject *A* in Plates 9-12, Figs. 10-17.)

FIG. 2. Healthy man, aged 20. (Subject *B* in Plates 9-12, Figs. 20-27.)

FIG. 3. Healthy woman, aged 55. (Subject *C* in Plates 9-12, Figs. 30-37.)

Types of stomach. It follows that, if neither of the two points between which the stomach lies and hitherto regarded as 'fixed' points are even approximately so, the shape of the stomach is likely to vary greatly. Moreover, the actual size of the organ that lies between the two points does not bear any definite relationship either to the build of the subject or to the distance between these two points. It is true, however, that certain *types* are commonly found in subjects of a certain build; for instance, the small hypertonic stomach is common in the man of short stature and prominent abdomen (Kretschmer's 'pycknic' type), while the long '*gastroptotic*' type is met with in tall thin women. It might be thought that the shape and disposition of the abdominal contents, such as is shown in Case *C* (Plates 9-13, Figs. 30-38), would only be found in tall thin women. Yet I have seen exactly the same condition in some of my men students. One of these, a man of sturdy athletic build, captain of his boat club, and in training for the races, had a stomach and colon which were almost a replica of subject *C*.

The radiologist of the early days had some difficulty in finding names for the forms of the stomachs that he saw, and he described them as J-shaped, fish-hook, steer-horn, &c. At that period clinical medicine was obsessed

with the 'conception of visceroptosis. Naturally, therefore, the long, or 'dropped', stomach was not considered to be normal and was labelled gastropptosis, or, if defective in tone (i.e. not holding up the contents in tubular form against the action of gravity), it was called an atonic stomach. Later, however, the radiologist was disturbed by the fact that the form described one day might be quite different the next. Moreover, it was not a fixed shape, for it was easily altered by manipulation of the abdomen or the pressure of intra-abdominal structures, or even by gas in the intestine. Little wonder, then, that these shapes are markedly affected by posture and by respiration, and that surface markings are apt to give a false impression of forms that may be transitory.

The *small stomach*, often called the 'hypertonic' type of stomach, does not differ essentially from the generally accepted normal; it is proportionately shorter and wider, and the pylorus and first part of the duodenum pass more or less transversely, or even downwards, into the second part of the duodenum. The pylorus in these cases may be on the level of the twelfth dorsal vertebra, so high that palpation is impossible because of the costal margin.

In *infants* the stomach is comparatively spherical, and it does not elongate till the erect posture is assumed, and even then it only gradually assumes the adult form.

In *children* it is relatively shorter and wider in proportion to the length of the body. Whereas in the adult the stomach usually reaches the umbilicus, in children it does not reach the umbilical level and assume a J-shape till near puberty.

Plate 9, Figs. 11, 21, and 31. *Erect position—lateral view.* With the rays passing from side to side, we see the stomach more or less as in section. Its axis slopes from above downwards and forwards at an angle which varies with the form of the lumbar curve. The average angle in 100 consecutive cases was nearly 30° (as in Subject *A*). In persons with the marked lumbar curvature it is nearer 45° (as in Subject *B*). With the long type of stomach there is hardly any angle at all; it merely curves gently round the kidney (Subject *C*).

The shadow outline of the stomach is not, however, a true section view, for the lower part of the stomach is straddled across the vertebral column, and the 'section' does not give a true idea of its antero-posterior thickness.

The Effects of Respiration on the Stomach

Plate 10, Figs. 12, 22, and 32. On deep *inspiration* the lower border of the stomach does not descend to anything like the same extent as the cardia. This is due to a 'concertina' type of action in the stomach muscle, presumably controlled by muscle tone, which tends to counteract the effect of the excursion of the diaphragm. In the J-shaped stomach—the most common type met with—this action compensates almost completely for the downward diaphragm movement of inspiration. Where, however, the tone of the gastric muscle is diminished, we note a degree of movement of the lower part of the stomach-shadow almost, if not quite, as great as that of the diaphragm.

This fact may even serve as a rough gauge of the degree of atony of the stomach. When marked atony (or 'gastroptosis') is present, however, the lower border of the stomach rests on the pelvic contents, and there is practically no movement on deep inspiration (Plate 9, Fig. 31). The greatest degree of downward movement in response to inspiration is in those stomachs that present a relatively slight degree of atony, i.e. where the concertina action is impaired, but where the lowest part is still well above the pelvic floor.

A curious and unexplained feature in Plate 10, Fig. 32, is the fact that the fundus appears to leave the diaphragm, whereas in deep expiration (Plate 10, Fig. 33), with the diaphragm high up in the chest, the fundus occupies its usual position under the dome of the diaphragm. This may be due to the spleen being pressed in between the stomach and the diaphragm in some way, for the same feature is noted with this subject at rest supine (Plate 11, Fig. 34). There is some support for this suggestion from the lateral supine picture (Plate 11, Fig. 35), in which the fundus does not seem to lie so far back in the abdomen. It will be noted that the fundus leaves the diaphragm to a greater or lesser extent in all three subjects when they lie on the right side (Plate 12, Figs. 17, 27, and 37), and perhaps this may be explained in the same way.

The pictures of the stomach on forced *expiration* (Plate 10, Figs. 13, 23, and 33) show an extraordinary upward excursion of the whole stomach. After seeing the effectual way in which the concertina action compensates for the movement of deep inspiration, one might expect to find a corresponding relaxation of the gastric muscle in expiration which would stabilize the position of the lower part of the stomach. I have, however, seen little evidence of this. Whether it is due to the absence of relaxation of the stomach wall or to the action of the abdominal muscles in the forced expiratory effort I do not know, but in ordinary unforced respiration one sees only a slight degree of this upward displacement.

The change of shape of the stomach in deep expiration approximates closely to that seen in the recumbent posture, and, curiously enough, the technical distortion already noted happens, in this picture, to make the diaphragm level 'at rest' appear as high as at the maximum on deep expiration.

It should be noted that the effect of forced respiration on the viscera is not uniform and depends on the type of respiration. The changes are more marked in subjects in whom the abdominal type of respiration predominates.

It is easy to give a dramatic demonstration of the great mobility of the stomach and other abdominal contents. I arrange with the students for one of the class to have his stomach and colon filled by an opaque meal. With the aid of a looking-glass he notes the effect of deep respiration on the shadows of these two organs. The movement, combined with the amusement of the class, usually makes him laugh, and the hilarity results in vigorous and jerky contractions of the abdominal muscles, to which the organs respond in an appropriate manner! The most mirth-provoking movements are, however, produced when the subject voluntarily retracts

and protrudes his abdomen. In response to this movement, suggested by Dr. R. S. Paterson, the organs almost look as though they had no attachments at all, and their range of movement is considerably greater than that of the diaphragm. The stomach and colonic flexures perform long excursions. In one instance, with the subject lying on the couch, I measured a nine inch excursion of the lowest part of the stomach. The hepatic flexure straightens out and rises several inches, and the transverse colon may move six inches or more. The whole abdomen behaves like a rubber bag, the contents of which can be displaced into any part by the squeezing of the muscles or in other more expressive words 'like a jumble of slithery things in a hole' (H. B. Fell). Even a caecum that is low in the pelvis has a range of movement that could not be effected by massage or manipulation of the abdomen. I am inclined to think that this might be employed for the detection of abnormal fixation. That laughter should have such an effect would seem to explain its close association with good digestion and plentiful adipose tissue! And the moral for thin people is not that they should eat more, but that they should laugh more, especially at and after meals!

Effect of Gravitation on Stomach Form

Plate 11, Figs. 14, 24, 34. *Recumbent position, postero-anterior view.* Adoption of the recumbent position is accompanied by a marked change in the shape of the stomach. The main feature is a narrowing and emptying of the pyloric end and a widening out of the cardiac end, because gravitation causes the food to slide into the cardiac end, leaving the pyloric antrum either empty or occupied by the air that fills the fundus in the erect posture. The length of the organ, from the fundus to the lowest part, is also diminished, and the pyloric end slides up on the posterior wall of the abdomen. The variation is best appreciated by comparing Plate 9, Figs. 10, 20, and 30 with Plate 11, Figs. 14, 24, and 34, and with the records of the position of the pylorus in Figs. 1, 2, and 3 (p. 264).

Plate 11, Figs. 15, 25, 35. *Recumbent position—lateral view.* In the recumbent posture, the rays passing from side to side, it will be seen that the food naturally gravitates into the cardiac end and leaves the pyloric antrum empty. The way in which the air from the fundus can distend the pyloric end should be noted. There happened to be a fair quantity of air in the stomach in each of these cases when the examinations were made. This shadow-picture does not represent a true section view owing to the straddling of the pyloric portion across the vertebral ridge of the abdomen. It was the percussion of this air in the stomach that gave such an unreliable guide as to the size of the organ in pre-X-ray days.

It is of interest to compare these pictures with the corresponding ones (Plate 9, Figs. 11, 21, and 31) taken in the erect position. The spinal curves flatten out when the subject lies on the back, a change which is largely responsible for the shape that the organ takes up. The greater the lumbar

curve, the greater is the tendency for the cardiac end to fall backwards and drag the pyloric end up over the kidney and pancreas.

Plate 12, Figs. 16, 26, and 36. *When the subject lies on the left side.* The stomach sags down into the left flank, dragging with it the pylorus and duodenum. The greater curvature is moulded to the contour of the left flank of the abdominal cavity, while the lesser curvature sweeps down from the cardiac orifice and then up again to whatever position the pylorus has assumed. It is not, of course, a routine position in gastric examinations, but I once observed a subject in whom the pylorus was actually over the left kidney when he lay in this position. I am satisfied that the weight of the opaque food will not account for more than a fraction of the distortion of the shape of the stomach. The figures reproduced would be almost identical had they been obtained with ordinary food instead of an opaque meal.

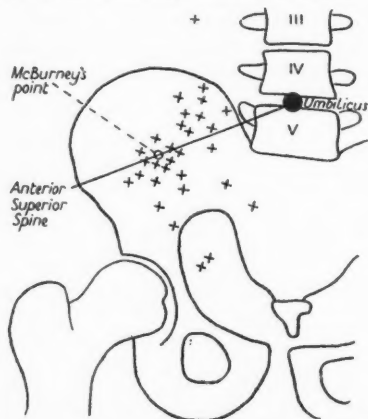


FIG. 4. The position of the caecal end of the appendix, traced in from thirty unselected cases radiographed in the horizontal position.

The way in which the diaphragm tilts in this posture should be noted, though it should be borne in mind that, since the central ray is at some distance from this point, the radiograph exaggerates the apparent movement.

Plate 12, Figs. 17, 27, and 37. *With the subject lying on the right side.* The pyloric end of the stomach comes right across the middle line in all these cases, and one would imagine that the duodenum must be kinked. Yet this is the accepted position for aiding digestion, and obviously there can be no actual kinking: the duodenum adjusts itself to the position. The cardiac end of the stomach is pulled out from the dome of the diaphragm, and I do not know what replaces it. The tilting of the diaphragm is again present, but it is not so marked as when lying on the other side.

Caecum and Appendix

The position in which the radiologist finds the caecum varies within rather wide limits. It is obviously capable of very extensive displacement

in response to posture, respiration, and manipulation. In Fig. 4 I have plotted out the positions of the caecal end of the appendix in thirty unselected cases, with the patients in the supine position. The majority are found about McBurney's point: the junction of the middle and outer thirds of a line drawn from the anterior superior spine to the umbilicus. In the upright position, however, the appendix lies on an average two or three inches below this point. In my tracings, the positions in which the caecal end of the appendix were found are covered by a circle seven inches in diameter centred on McBurney's point. It must be emphasized, however, that nearly all the radiographs were taken under the abnormal condition produced by the pressure that is usually necessary to visualize the appendix. The diagram is, therefore, more an indication of range of mobility than of actual position.

Large Intestine

The whole of the large intestine, including the caecum and sigmoid, moves with forced respiration, and the flexures have almost, if not quite, the same range of movement as the diaphragm. Generally speaking, however, the farther away the viscus is from the diaphragm the less is the movement in response to respiration.

Posture affects the whole of the large intestine, as is illustrated in Plate 13. The same three subjects and one additional man were used, and, even in these few unselected cases, the variations both in normal position and in the range of movement of the flexures due to posture are very striking, quite apart from the added excursion that is due to respiration, which I have not attempted to figure. As already described, forced and jerky movements of the abdominal muscles cause the colon and other abdominal viscera to move in a manner that can hardly be described as anything less than acrobatic.

The usual position of the hepatic flexure in the standing position is an inch or a little more above the iliac crest, while on lying down it usually rises some two to three inches higher. The flexure itself looks like an acute angle, but this appearance is, of course, due to foreshortening.

In the majority of cases the splenic flexure is found high up, in the position indicated in the anatomy books, but about a third of the students examined present splenic flexures that are considerably lower. Occasionally we find the splenic flexure only just above the iliac crest in the erect posture.

The position of the transverse colon is very variable. In the two women of my series it happens to be low down in the pelvis, and on the whole I think one finds it lower in the female than in the male, but it is far from uncommon to find the same low position in men who are in perfect health and in training for sports of one kind or another. In fact muscular development does not appear to be a controlling factor at all. The varieties of transverse colon encountered are legion; the only variety not seen is one that is actually 'transverse'! In most cases we find a festooned loop, often with a subsidiary festoon that drops down almost, if not quite, into the pelvis. The position in the upright posture depends entirely on the stomach,

for the colon hangs from it, attached by the transverse meso-colon. Hence, if the stomach becomes atonic and drops, the colon likewise drops. It would have been better if the concept of coloptosis had been abandoned before it had any chance of being thrust upon a confiding public, for it has given rise

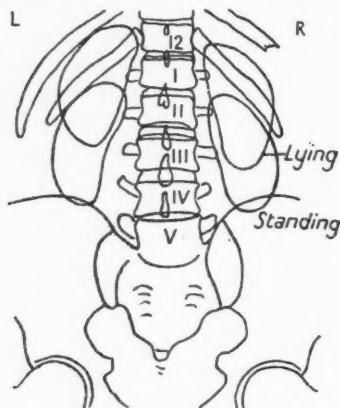


FIG. 5.

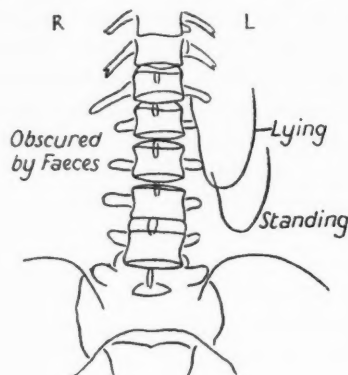


FIG. 6.

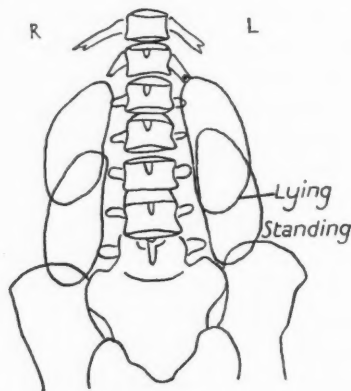


FIG. 7.

The effect of posture on the position of the kidneys. The upper kidney outline is traced from a radiograph taken in the horizontal, the lower from an exactly comparable one taken in the upright position.

FIG. 5. A healthy man, an artisan, aged 45.

FIG. 6. A healthy woman, a nurse, aged 27.

FIG. 7. A healthy woman, a clerk, aged 37.

to endless misinterpretation of normal phenomena. It is surely unnecessary to labour a point which is obvious to any one who sees a reasonable number of normal healthy subjects and studies them with an open mind.

Other Abdominal Organs

Presumably the *pancreas* is the least mobile organ in the abdomen, but it cannot be seen radiographically. All other organs are movable to a greater

or lesser extent in response both to diaphragmatic movement and to gravitation. The *kidneys* are not readily seen on the fluorescent screen, but the outline is visible on radiographs. Until the last few years some device for compression and fixation against respiratory and other movements, during the exposures, was essential in order to show the kidney, and consequently the outline was always in a higher position than it would normally occupy. Compression is no longer needed, and we find that an excursion of an inch or more in a direction downwards and outwards, parallel with the edge of the *psoas*, is normal in response to respiration.

I asked a friend to radiograph a normal subject, and expose films both in the standing and lying postures under identical conditions as regards respiration. He selected a workman of average build, about 45 years of age. A tracing of the bony parts showed that these films had been taken in exactly the same position, except for the posture of the subject. On this tracing the kidney outlines, which were clearly seen in both films, were filled in, and the result is shown in Fig. 5, and the difference recorded in position of the kidneys, due entirely to posture, is far greater than I ever expected. Accordingly, I made similar observations on two other subjects (Figs. 6 and 7), and found a degree of movement of the kidneys that was slightly more in one and slightly less in the other than that shown in the first subject. These subjects were healthy young women of small build. So far as I can see, however, the kidneys are not so subject to movement from respiration as from posture. Nor do they appear to be displaced by violent movements of the abdominal muscles to anything like the same degree as the stomach and intestines.

The *liver* is subject to the full range of diaphragmatic movement, and it is also affected by gravitation. In the days when pneumoperitoneum was being explored as a diagnostic radiographic method, the whole outline of the liver was well shown, and the displacements that occurred without any untoward results were remarkable.

I endeavoured to record the movement in one subject, a middle-aged woman with a lax abdomen, many years ago. Lantern slides made at the time are the only records available. I distended the colon with air, and in this way defined the liver outline quite sharply. Perhaps the technique had some effect on the mobility, but posturing caused very extensive movements of the liver. These are recorded in a composite tracing made from the lantern slides (Fig. 8).

It is a remarkable fact that in the radiography of the *gall-bladder* for diagnostic purposes its position is found to vary within very wide limits. On the average it approximates to the orthodox anatomical position, but it is sometimes found considerably higher and very often lower than would have been considered possible, even considering the possibility of hepatic enlargement. Not infrequently we find the gall-bladder actually overlapping the shadow of the crest of the ilium, and even in the pelvis. The liver is undoubtedly much more mobile than we would expect.

The *spleen* is not seen on an X-ray film in ordinary circumstances, and I have no observations on its movements. It must, however, move with the diaphragm, and, clinically, we know that it is often palpable and that, when felt, it can be easily displaced. Moreover, we know that a spleen which is palpable with the patient standing is sometimes not felt when the patient lies down.

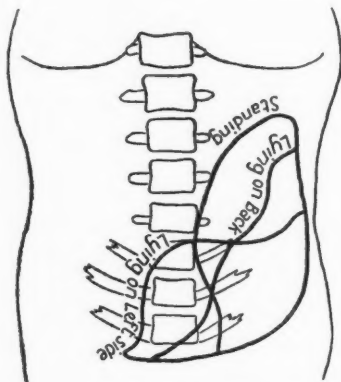


FIG. 8. The movements of the liver as the result of posture.

(a) The outline with the patient standing; (b) the outline with the patient lying on the back; (c) the outline with the patient lying on the left side.

The tracings were made from radiograms taken many years ago after inflating the bowel with air, and were regarded, at that time, as showing an extreme degree of pathological mobility. The subject was a middle-aged woman with lax abdomen. It seems likely that the degree of mobility demonstrated is not extreme or unusual and might be found in many healthy subjects.

A technique for visualizing the spleen and liver has been devised (45), but I have no experience of it. It consists in the intravenous injection of thorium dioxide (thorium: atomic weight 234.4). This salt is said to have an affinity for reticulo-endothelial cells, and it is taken up so freely by the liver and spleen that a satisfactory radiogram can be obtained. With this technique it should be easy to obtain records of the movements under normal conditions.

Discussion

Many radiologists have probably conceived the idea of revising the anatomy of the abdomen in the light of X-ray observation, so as to give a satisfactory idea of the 'living stomach' and other organs, but their book still remains unwritten.

I once made a series of plaster casts of what I then considered to be 'the normal stomach', showing the influence of posture on the shape of the organ (9). They are still of assistance in giving the student a grasp of the general contour of the organ that gives the shadow-picture on the fluorescent screen. But the models have the defect that must be associated with every attempt to crystallize ideas of the 'normal stomach', viz. that

the terms of orthodox anatomy are not applicable to descriptions of the conditions of life; the symbols of our formulae are unrelated to the actual facts. They may be correct as regards the dead subject, which, unfortunately, is the anatomy that is still taught to the medical student, but they are quite inapplicable to the subject which the clinician has to deal with.

Descriptive terms and diagrams can at best only indicate a given phase of form or relationship. The difference between orthodox anatomy and actual conditions is something like that between an ordinary photograph, which gives a fixed and unchanging picture, and a cinematograph picture, which is a succession of ordinary photographs that portray the movement and change that are essential living factors. A cinematograph record, however, is still a long way from recording the living organ, for a true conception of the living organ would take into account a dozen other factors, such as the influence of the mind on the body, to which the changes in form and function of the abdominal organs are merely the response. The death-mask of Napoleon gives little clue to the living face of the man as he watched and directed his armies, or of those inscrutable eyes, the colour of which none could describe after he had gone.

Further, we should not look upon the stomach or any of the abdominal viscera as entities that can be studied individually and separately, any more than we can take one sentence out of its context and expect to get an idea of the whole chapter. The anatomy of a living organ—and, for that matter, its function also—is an expression of many influences both in the organ itself and elsewhere. We are, in fact, justified in regarding the stomach as one of the most responsive organs in the body, for we know that it may react to almost every emotion and sensation that man is capable of experiencing (7 A). Perhaps it may seem that I am exaggerating the importance of this outlook, but surely it is one that is far less cramping to the understanding of the living, moving, responsive anatomy and physiology of the abdomen than that to which we have been accustomed.

Surface markings that give the student a mental picture of fixed positions cannot be satisfactorily applied to the essential changefulness of the conditions in life, but, unfortunately, no other method of description is available. True, in a given posture, each organ has a relative position in regard to other organs, and is usually found in this position. But, although Nature has a definite plan, she has infinite varieties of design, so that all sorts of variations are possible. She provides a veritable kaleidoscope of balanced form and function. I have yet to learn the limits that Nature sets to the bounds of normality.

In recent years it has been my lot to examine many healthy students, and I have been increasingly impressed with the need of regarding the anatomy of the abdominal viscera as 'fluid'. There is no set and standardized design; divergences from the average are common. Some of these are extreme, yet the subjects have been healthy male and female students.

There is much food for thought for clinicians in these observations, for, had I been examining these subjects with a view to discovering the aetiology of some complaint, I could not have resisted the temptation to claim such divergences from the average as the obvious cause of their symptoms.

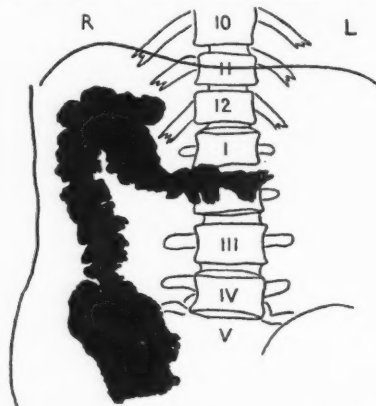


FIG. 9. Tracing of radiograph showing the disposition of the caecum and ascending colon found in a healthy student. The hepatic flexure lies *behind* the liver.

To take an extreme instance: suppose a radiologist was investigating a case of constipation, and found such a state of affairs as I have indicated in Fig. 9—a caecum deep down in the pelvis with an ascending colon of more than double the usual length extending up into the dome of the diaphragm; and the hepatic flexure in a mysterious position behind the liver, housed in the peritoneal pocket, a potential space, that runs up behind the liver as far as the bare area! Absurd to suppose it possible for the food to pass on without obstruction in such circumstances! Surely it could not have room in such a confined space, and, even if this was admitted possible, the intestine must be 'kinked' as it entered or left this space and found its way round the posterior lower edge of the liver and up to what appeared to be a normally placed splenic flexure! Could any radiologist have resisted putting such an obvious two-and-two together, and could any surgeon have doubted the propriety and expediency of adjusting such a gross and obvious source of the trouble? Yet the condition was present in a perfectly healthy student, who did not suffer from constipation and was apparently normal in every respect. The condition is, presumably, what we would call a developmental abnormality, but why development should have allowed this freak is difficult to imagine. There is little doubt that all the older workers, radiologists, physicians, and surgeons alike, being entirely ignorant of the extraordinary elasticity of Nature's mechanics, have often fallen into such traps which snare those who look for simple mechanical explanations of symptoms.

To the three subjects who lent themselves ungrudgingly to this study, the many students on whom I have made observations, to Sir Humphrey

Rolleston, Dr. F. G. Spear, Dr. W. Bain, Dr. Meyrick-Jones, and to Mr. H. P. Hudson, who has given much help in the photographic technique, I tender my grateful thanks.

Conclusion

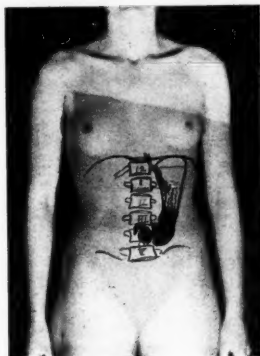
In this paper is recorded a study of the effect of posture and of forced respiration on the abdominal viscera. Composite pictures are reproduced showing the displacements and distortions. These indicate that in normal subjects the abdominal organs are not fixed, and that they have a wider range of movement, both in relation to the abdominal wall and to each other, than might be expected. The illustrations record the mobility and indicate the 'fluid' character of the anatomy of the abdominal viscera.

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Standing, At Rest
Post.-Ant.



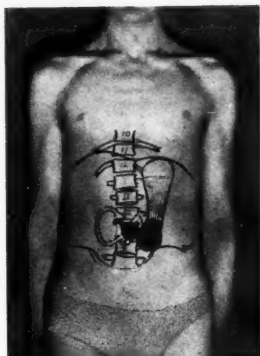
10

Standing, At Rest
Lateral



11

Subject A
Woman aged 27
5 ft. 5 in.
118 st. 6 lb.

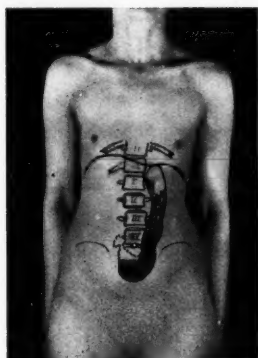


20



21

Subject B
Man aged 20
5 ft. 9½ in.
111 st. 3 lb.



30



31

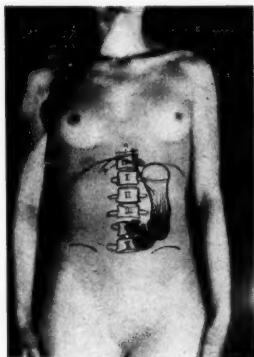
Subject C
Woman aged 55
5 ft. 7½ ins.
8 st. 10 lb.

STOMACH OUTLINES IN THREE HEALTHY SUBJECTS
Mid-phase of respiration

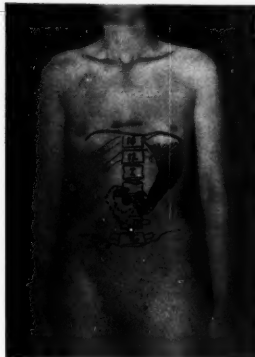
Standing, Full Inspiration

Standing, Full Expiration

Subject A

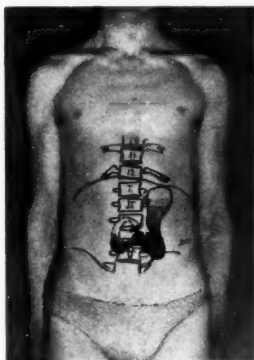


12

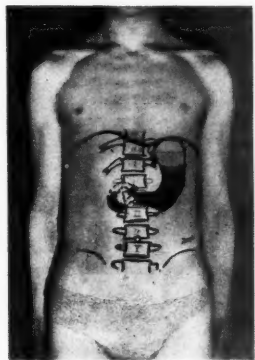


13

Subject B

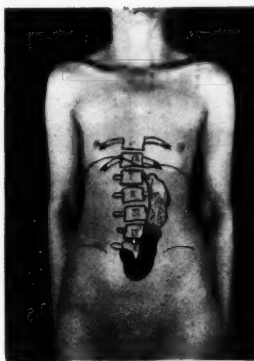


22

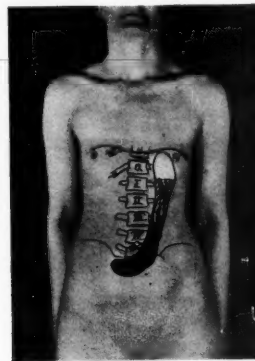


23

Subject C



32



33

The effects of forced respiration on the stomach in the same subjects

Quart

Su

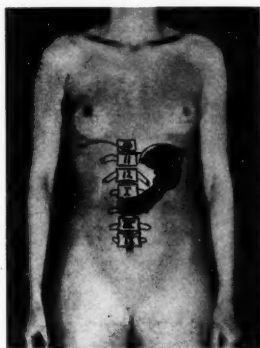
Su

Su

Lying Supine
At Rest

Lying Supine
At Rest

Subject A

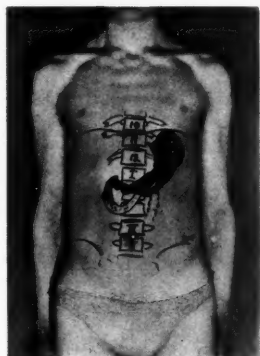


14



15

Subject B

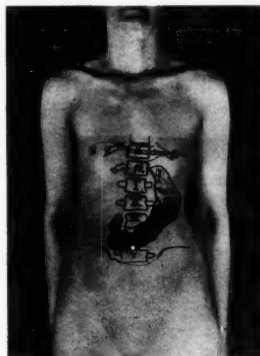


24



25

Subject C



34



35

The effects of gravity on the stomach in the same subjects

Quarte

St

S

S

Lying on the Left Side
At Rest

Lying on the Right Side
At Rest

Subject A

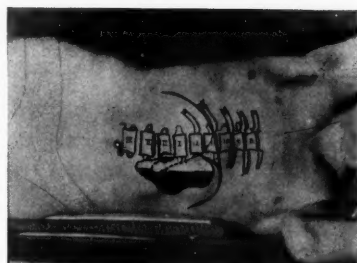


16

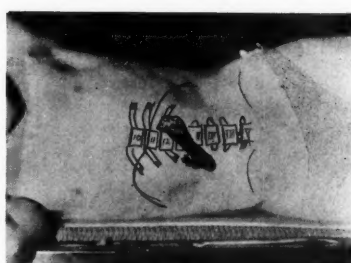


17

Subject B

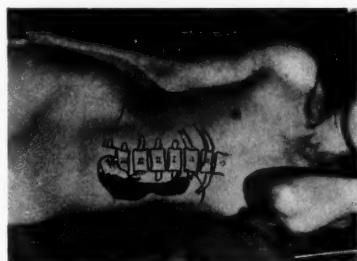


26

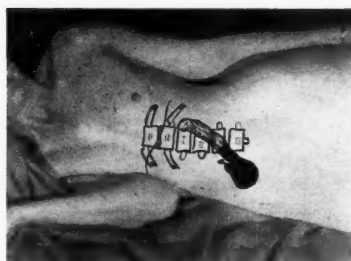


27

Subject C



36



37

The effects of gravity on the stomach in the same subjects

Subject A

Fig. 18

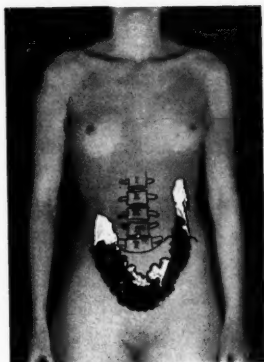
Subject D

Fig. 19

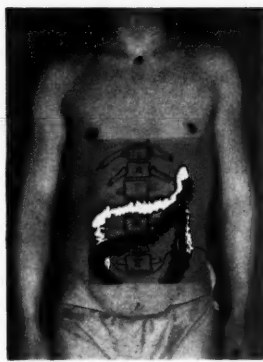
Man aged 20

5 ft. 10½ in.

1 st. 3 lb.



18

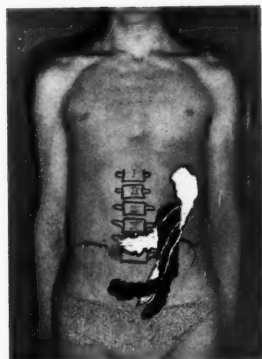


19

Subject B



28



29

Subject C



38

The effects of gravity on the position of the colon.
Tracings of the filled colon.
(1) Standing (black)
(2) Lying supine (shaded)
In each case the radiograms were taken in the mid phase of respiration.

The effects of gravity on the colon in the same subjects and one other (fig. 19)

THE ELECTROCARDIOGRAM IN DIPHTHERIA¹

By STANLEY ALSTEAD

(From the Birmingham City Hospital, Little Bromwich)

With Plates 14 to 17

INTEREST in electrocardiographic records during diphtheria has mainly centred around the gross lesions of the myocardium or specialized conducting system of the heart which are commonly supposed to account for, or contribute to, death in this disease. Stecher (1) in two papers has described the various grades of heart-block found in diphtheria. Theories to account for the mechanism of circulatory collapse in diphtheria have been supported or refuted by various methods of investigation, and in recent years the information afforded by the electrocardiograph has been widely discussed. Reference to the literature shows, however, that when the electrocardiograph has been used in attempts to solve this problem, the results have been as unsatisfactory as most other approaches to the subject. Nathanson (2) commented on the lack of agreement between various workers as to the cause of circulatory failure in diphtheria and expressed the view, based on his own clinical and electrocardiographic investigations, that the changes in the heart-muscle were in themselves sufficient to account for death. Marvin (3), though substantially in agreement with this conclusion, admitted the possibility of primary failure in the peripheral circulation, the latter condition sometimes being independent of any change elsewhere.

During the past five years a considerable number of clinical and electrocardiographic records in diphtheria have been collected in the Birmingham City Hospital, in which eight of the main diphtheria wards are wired to the electrocardiographic department.

The object of the investigation to be described was to attempt to define the changes commonly seen in the electrocardiogram in the course of diphtheria, to correlate them, as far as possible, to the clinical condition, and to assess the value of this instrumental investigation in a fever hospital.

One hundred cases were taken, representing three types: mild (23 per cent.), moderate (32 per cent.), and severe (45 per cent.) cases. This classification was only comparative, and was based on serum-dosage. The clinical abnormalities which were taken to indicate diphtheritic myocarditis were those widely accepted by most writers, namely: 1. Persistent tachycardia or bradycardia. 2. Heaving cardiac thrust on palpation. 3. Movement of

¹ Received November 21, 1931.

the apex-beat to a position farther away from the midline than on previous examination of the heart. 4. Changes in the character of the heart-sounds, especially softening of the first sound at any area, particularly the mitral area, or duplication or splitting of the first mitral sound, or excessively loud or booming heart-sounds. 5. Alteration in the heart rhythm to a 'triple' or 'gallop' type (usually associated with a duplication of the first sound). 6. Deterioration of the general condition of the patient, characterized by pallor, abnormal restlessness or apathy, vomiting, enlargement of the liver accompanied by abdominal tenderness; rapid, easily compressible pulse, and fall in blood-pressure. 7. Abnormal response to increasing physical effort as indicated by the pulse-rate. If extra-systoles and sinus arrhythmia appear during the course of diphtheria or are very much aggravated by the disease they are probably the result of active pathological processes in the heart, but in the usual case it is the general opinion that they do not indicate, of themselves, any serious degree of generalized myocarditis. This conclusion is in agreement with the present findings.

In the electrocardiogram the abnormalities commonly found are (i) conductive lesions of varying severity, namely intraventricular block, bundle-branch and complete auriculo-ventricular dissociation, and (ii) a group, less clearly defined, of lesions myocardial in origin without gross involvement of the specialized conducting system. The latter are seen in their earliest stages as a 'slurring' of the *R*-wave with a consequent alteration in the form of the *ST* line. A more advanced condition of degeneration is indicated by biphasic changes in the *T*-wave and, lastly, complete inversion of the *T*-wave in significant leads is regarded as evidence of considerable myocardial damage. Combinations of 'conductive' and 'myocardial' types of lesions are, of course, not infrequent. When the electrocardiogram is normal except for inversion of the *P*-wave in one or more leads, inversion of the *T*-wave in Lead III, bizarre *QRS* complex in Lead III, or ventricular preponderance, the records show that, unless these abnormalities have appeared in the series of records as a result of the disease, the clinical condition of the heart is satisfactory and the electrocardiographic abnormality can be disregarded.

The following electrocardiograms have been selected from some of the series of records obtained in the cases investigated and are intended to illustrate the onset of various types of lesions.

Case 5. Electrocardiogram No. 1. (Aged 10 years.) Plate 14, Fig. 1. *Observations:* Heart-rate 120 per minute. Action regular. Low voltage in Lead I. *P*-wave frequently inverted. 'Slurring' of the descending limb of the *R*-wave occasionally merging into a biphasic *T*-wave in Lead II. *P-R* interval 0.14 sec. *QRS* 0.05 sec. in Lead I; other leads indefinite. *Interpretation:* Tachycardia associated with a moderate degree of myocarditis. *Clinical condition:* Apex-beat of the heart in fifth intercostal space overlapping the left nipple-line. Some degree of softening of the first mitral sound was present, but both sounds were well heard and the heart rhythm was normal.

A more advanced stage of myocardial degeneration demonstrated by electrocardiograph is to be seen in the sixth tracing of a series in the investigation of Case No. 32 (aged 4½ years). Plate 14, Fig. 2.

Observations: Heart-rate 100 per minute. Action regular. *P-R* interval 0.12 sec. *QRS* 0.06 sec. Well-marked slurring of the *R*-wave in Leads I and III. *Interpretation:* Fairly advanced degree of myocarditis and slight delay in intraventricular conduction. *Clinical condition of the heart:* Apex-beat in the fifth left intercostal space well inside the nipple-line. Heart-sounds regular and distinct, but the first mitral sound was duplicated: rhythm normal.

The next stage of myocardial damage was present in ten of the cases, all of which except one were classified as 'severe' on clinical grounds. With the exception of two of these cases, where the *T*-wave was negative in two leads only (II and III in both) an inverted *T*-wave was seen in all leads of the electrocardiogram in the course of the disease.

In general, the clinical signs corresponding to this electrocardiographic abnormality were a gross deterioration in the quality and volume of the heart-sounds, the first sound at all areas, especially the first mitral sound, being softened and, at times, almost inaudible. This was accompanied by alteration in the position of the apex-beat in two cases, varying degrees of tachycardia and, occasionally, signs of the congestive type of heart-failure. In a few of the cases it was found that when there was a sudden onset of symptoms and signs of heart-failure the electrocardiogram did not appear to give a true representation of the severity of the condition, only the early indications of myocardial degeneration being discovered in the record. Later developments tended to show, however, that the electrocardiograph had accurately demonstrated the extent of the cardiac damage at the time, but the general disturbance appreciated clinically was probably due to the shock of onset of the complication upon the cardiovascular system as a whole rather than the intrinsic effect of the lesion in the heart. This view applies to the myocardial lesions as distinct from disease principally affecting the specialized conducting system, as in the latter type the electrocardiographic diagnosis almost invariably anticipates the clinical one whether relating to the time of occurrence or to the exact site of the lesion.

In these cases, improvement in the physical signs in the heart and general condition of the patient is usually accompanied by a gradual reversion of the *T*-waves to the normal shape and direction. All of the ten cases mentioned above made a complete recovery, and during the past five years no cases which, on investigation, were found to be of this type ended fatally. Sudden death in convalescence has, however, been recorded in similar cases by Marvin (3) and by Nathanson (2), both of whom discuss the value of the electrocardiograph in controlling treatment and convalescence in cases of diphtheria. It must be emphasized that a normal record in the course of a series in which the signs of severe myocarditis have been present is not in itself sufficient. The 'stability' of the *T*-waves should be verified over

a period of two or three weeks before increasing the work to be done by the heart, as it is often found that the condition of the myocardium is liable to relapse with the onset of diphtheritic paralysis or appearance of septic foci anywhere in the body, and sometimes for no apparent reason.

The following case is typical of this group and will be described in relation to some of the electrocardiograms selected from a series obtained from the onset of cardiac complications to the time when recovery was almost complete.

The age of the patient was ten years, and she was admitted on the fifth day of disease. There was considerable oedema of the fauces, extensive deposits of membrane in the throat and post-nasal space, and bilateral cervical adenitis. In addition to 8,000 units of antidiphtheritic serum given intramuscularly before admission to hospital, 88,000 units were injected intravenously with a 50 per cent. solution of dextrose. Glucose was given by mouth and the patient received insulin daily.

Case 41. Electrocardiogram No. 1. Plate 14, Fig. 3. 13.10.30. Observations: Rate 180 per min. Action regular. Low voltage in Lead I. *T*-waves positive in Lead I and Lead II: negative in Lead III. *P-R* 0.1 sec. *QRS* 0.04 sec. *Interpretation:* Suggests onset of myocardial changes, but may be normal for the individual. *Clinical condition of the heart:* Apex-beat just within the nipple-line. Heart-sounds regular; first sound not well defined and the second sound accentuated at all areas.

Electrocardiogram No. 3. Plate 14, Fig. 4. 18.10.30. Observations: Rate 120 per minute. Action regular. *P-R* 0.12 sec. *QRS* 0.06 sec. *T*-waves positive in all leads. Moderate degree of 'slurring' of the *R*-wave in all leads. Recovery of voltage. *Interpretation:* Myocarditis established. *Clinical condition of the heart.* Centre of the apex-beat in the nipple-line and the fourth left intercostal space. Heart-sounds regular and distinct, but the first mitral sound was duplicated. Rhythm normal.

Electrocardiogram No. 5. Plate 14, Fig. 5. 21.10.30. Observations: Rate 100 per min. Action regular. *P-R* 0.12 sec. *QRS* 0.06 sec. *T*-wave positive in Lead I; biphasic in Leads II and III. *R*-waves slurred in all leads. Slight fall in voltage. *Interpretation:* Myocarditis increasing. *Clinical condition of the heart:* Heart-sounds well defined and action regular.

Electrocardiogram No. 12. Plate 14, Fig. 6. 7.11.30. Observations: Rate 120 per min. Action regular. *P-R* 0.12 sec. *QRS* 0.04 sec. *T*-wave negative in all leads. *R*-wave well defined. Low voltage in Lead I. *Interpretation:* Considerable myocardial damage. *Clinical condition of the heart:* Apex-beat interval to the nipple-line. Occasional extra-systoles and the first mitral sound was blurred.

Electrocardiogram No. 14. Plate 15, Fig. 7. 29.12.30. Observations: Rate 120 per min. Action regular. *P-R* 0.12 sec. *QRS* 0.04 sec. *T*-wave positive in Leads I and II, negative in Lead III. *R*-wave well defined. Voltage normal. *Interpretation:* Electrocardiographic recovery. *Clinical condition of the heart:* Heart-sounds quite satisfactory.

The selection of electrocardiograms is sufficient to show the gradual deterioration of the heart-muscle and, finally, a satisfactory degree of recovery. An interesting feature in the complete series was a sudden relapse in condition of the heart electrocardiographically as well as clinically with the onset of palatal paralysis.

Conductive Lesions

A considerable variety of conductive lesions is to be found in the course of diphtheria, and the diagnosis of these conditions, except in the most advanced cases where complete auriculo-ventricular dissociation is present, can only be made by the electrocardiographic method.

The early changes in the *P-R* interval which are commonly associated with the chronic forms of myocarditis such as rheumatism and syphilis are relatively rare in diphtheria: an increase in the time required for an impulse to pass from the sino-auricular node to the point where the bundle of His divides into its main ventricular branches is not often seen. It is necessary to take into account the increased rate of the heart in the early stages of the disease, but it has been found on examination of serial records in about 200 cases that the *P-R* interval is almost invariably less than 0.2 sec. In only one case did the *P-R* interval reach the arbitrary normal limit of one-fifth of a second; at one stage of the illness the measurement actually exceeded 0.2 sec. but then rapidly diminished to approximately 0.12 sec. Several cases, however, showed a *relative* increase in the *P-R* interval. Thus in one patient the initial value of *P-R* was 0.1 sec. and this increased to 0.12 sec. although the heart-rate was unchanged. The fact that the power of the auricular muscle and *a-v* bundle to conduct the cardiac impulse in the early stages of the disease was impaired can be deduced from a consideration of the following cases:—

P-R Interval

Case No.	Initial value with relatively fast heart-rate.	Value with relatively <i>slow</i> heart-rate during convalescence.
	secs.	secs.
25	0.10	0.08
35	0.16	0.12
46	0.14	0.10
68	0.14	0.12
82	0.12	0.08
88	0.12	0.10
89	0.12	0.12
93	0.12	0.08

It would appear, therefore, that in a small group of cases (ten in this series of 100 cases) diphtheria causes delayed conduction above the level of the auriculo-ventricular node but not to a greater extent than could be accounted for by the tract sharing the degenerative changes taking place at the same time in the surrounding myocardium. Bundle-branch block and complete heart-block are seen fairly frequently in the severe or untreated cases of diphtheria, and this fact makes it all the more surprising that a preliminary stage of widening of the *P-R* interval is so seldom seen to any appreciable degree.

Not infrequently the only part of the conducting tract to be affected is the Purkinje system in the walls of the ventricles. This intraventricular

block is demonstrated by widening of the *QRS* complex and splintering of the summit of the *R*-wave, and may occur independently of any changes in the *T*-wave of the ventricular complex.

The following is an example of a patient who developed intraventricular heart-block :

W. P., male, aged 5. Plate 15, Fig. 8. Advanced faucial diphtheria. Extreme toxæmia and collapse made intravenous therapy impossible : 56,000 units of antidiphtheritic serum given intramuscularly : subcutaneous saline : glucose by mouth. Later, dextrose intravenously and insulin. Satisfactory electrocardiograms were unobtainable in the early stages owing to restlessness ; two leads of one record are, however, reproduced and show : regular action of the heart ; rate about 140 per minute : *P-R* 0.1 sec., *QRS* 0.04 sec. *T*-wave positive in both leads : low voltage in Lead I.

Interpretation : Except for tachycardia the record is normal. *Clinical condition of the heart* : Apex-beat within the left nipple-line. Heart-sounds : only moderate volume, but quality unaffected.

Electrocardiogram No. 4. Plate 15, Fig. 9. *Observations* : Rate 160 per minute. Action regular. *P-R* 0.1 sec. *QRS* 0.1 sec. *T*-waves negative in all leads. Recovery of voltage. Splintered *R* in Lead III. *Interpretation* : Delayed conduction in the walls of the ventricles, associated with a considerable degree of myocardial damage. *Clinical condition of the heart* : Position of apex-beat difficult to define. First sound at mitral and aortic areas almost inaudible ; other sounds of poor quality.

Electrocardiogram No. 15. Plate 15, Fig. 10. *Observations* : Rate 100 per min. Regular action. *P-R* 0.1 sec. *QRS* 0.04 sec. *T*-waves positive in all leads. *Interpretation* : Normal record with restoration of original conduction-time in the ventricle walls. *Clinical condition of the heart* : apex-beat within the nipple-line : cardiac thrust satisfactory : heart-sounds of good volume and quality.

These three records from the series show the onset of intraventricular block associated with gross clinical deterioration of the heart, and the restoration of normal conduction during convalescence.

Bundle-branch lesions are usually found in the more severe cases or those in which specific treatment was postponed or omitted. The condition, though almost invariably associated with signs of great constitutional disturbance, is not infrequently a transient abnormality during the course of the disease : the following is an example of such a case. The patient was a youth of 16 years. Antitoxin had been given before admission to hospital but too late (sixteenth day) to be of much value. Within a week of admission clinical signs of myocarditis appeared : the apex-beat of the heart was diffuse and feeble and the heart-sounds were very soft in quality. On electrocardiograph the following record was obtained :

Electrocardiogram No. 1. Plate 15, Fig. 11. *Observations* : Rate 90 per min. Action regular. *P-R* 0.14 sec. *QRS* 0.1 sec. Left ventricular preponderance. *T*-wave in opposite direction to the main ventricular deflection in all leads. Inverted *P* in Lead III. *Interpretation* : Right bundle-branch block.

Electrocardiogram No. 16. Plate 15, Fig. 12. *Observations* : Rate 120 per min. Action regular. *P-R* 0.14 sec. *QRS* 0.06 sec. *T*-waves positive in Leads I and II ; biphasic in Lead III. Bizarre *QRS* and variable *P*-wave

in Lead III. *Interpretation*: Electrocardiographic recovery. *Clinical condition of the heart*: Apex-beat within the left nipple-line: heart-sounds well defined (general condition much improved). *Comment*: The first electrocardiogram shows bundle-branch block; the sixteenth, taken six weeks later, is a normal record with no evidence of any conductive lesion.

When death in diphtheria is due to heart-failure, complete heart-block is often found in association with other changes in the circulatory system. Two cases are briefly described below in which complete heart-block developed and disappeared before death occurred from other causes. They represent what is commonly considered to be the severest type of disease of the conducting system. In many similar cases microscopic examination of the bundle of His, *post mortem*, has shown more or less complete disorganization of the fibres.

L. C., male, aged 14 years. Extensive faucial diphtheria: profuse blood-stained nasal discharge: marked bilateral cervical adenitis and left peri-adenitis: diphtheritic footor: obviously very toxic. Antidiphtheritic serum, 48,000 units intramuscularly and 128,000 units intravenously one hour later: dextrose intravenously: glucose by mouth and insulin daily.

Electrocardiogram No. 1. Plate 16, Fig. 13. *Observations*: Rate about 165 per min. Action regular. *P-R* 0.12 sec. *QRS* 0.04 sec. *T-wave* positive in all leads. Right ventricular preponderance. *Interpretation*: Record is within normal limits. *Clinical condition of the heart*: No abnormality detected.

Electrocardiogram No. 6. Plate 16, Fig. 14. *Observations*: Rate about 100 per min. Action irregular. Premature beats. *QRS* 0.1 sec. (Lead II). *T-waves* indefinite, but mainly biphasic. Dissociation of auricular and ventricular beats; auricular rate about 75 per min. and ventricular rate about 100 per min. *Interpretation*: Complete heart-block: delayed intra-ventricular conduction: advanced myocarditis. *Clinical condition of the heart*: Position of apex-beat unchanged: heart-sounds of poor quality; split first mitral sound; rhythm normal.

Electrocardiogram No. 10. Plate 16, Fig. 15. *Observations*: Rate 120 per min. Regular action. *P-R* 0.16 sec. *QRS* 0.06 sec. (Lead II). *T-wave* poorly formed in all leads. Low voltage, especially in Lead I. *Interpretation*: Auriculo-ventricular relationship re-established: slight delay in conduction time from auricle to ventricle, but *P-R* is within normal limits. Evidence of myocardial damage is less definite. *Clinical condition of the heart*: Apex-beat farther to the left of the midline: cardiac impulse diffuse; sounds clearly defined and of fair quality. *Comment*: A selection from a series of electrocardiograms is given to show the onset and disappearance of complete heart-block. There was no recurrence of this condition, but the patient died from diaphragmatic paralysis on the thirty-fifth day of the disease.

A. E. A., male, aged 13. Severe faucial diphtheria: only mildly toxic in appearance: heart apparently normal on admission. Antidiphtheritic serum: 56,000 units intramuscularly and 56,000 units intravenously. Glucose given by mouth: insulin daily.

Electrocardiogram No. 1. Plate 16, Fig. 16. *Observations*: Rate 120 per min. Action regular. *P-R* 0.1 sec. *P-* and *T-waves* negative in Lead III.

Interpretation: Record is within normal limits, but suggests the onset of myocardial damage. *Clinical condition of the heart*: No abnormality detected.

Electrocardiogram No. 3. Plate 17, Fig. 17. *Observations*: Action apparently regular. Ventricular rate 75 per min. Auricular rate 100 per min. *QRS* (Lead I) 0.1 sec. *T*-waves biphasic in Lead I, positive and very large in Leads II and III. *Interpretation*: Dissociation of auricular and ventricular activity due to complete heart-block. *Clinical condition of the heart*: Position of the apex-beat unchanged. Heart-sounds very 'distant' but well defined.

Electrocardiogram No. 9. Plate 17, Fig. 18. *Observations*: Rate 140 per min. Action regular. *P-R* 0.1 sec. *QRS* 0.06 sec. (Lead I) *T*-wave negative in Leads II and III; *P*-wave poorly formed in Leads I and III. *Interpretation*: Considerable myocardial damage, but normal auriculo-ventricular conduction. Slight intraventricular delay. *Clinical condition of the heart*: Position of the apex-beat unchanged. Aortic sounds of poor quality; mitral sounds well defined.

Comment: A transient condition of complete heart-block is recorded. Toxaemia steadily increased, but the last electrocardiogram (No. 11) taken six hours before death showed no recurrence of heart-block, although the clinical condition of the heart deteriorated during a series of convulsions which preceded death.

It is possible roughly to assess the value of this method of investigation. The figures in Table I below are based upon the analysis of 100 cases of diphtheria of varying severity and entailed observations, such as are described above, on about 600 separate electrocardiograms.

TABLE I

Severity of the case.	Mild.	Moderate.	Severe.
	23 %.	32 %.	45 %.
Clinical condition and electrocardiogram corresponding	6 cases (24 %)	14 (38 %)	21 (42 %)
Electrocardiogram exceeding clinical signs in the heart	13 cases (52 %)	11 (29 %)	12 (24 %)
Electrocardiogram preceding clinical signs in the heart	1 case (4 %)	3 (8 %)	7 (14 %)
Clinical signs in the heart exceeding electrocardiogram	No case	3 (8 %)	5 (10 %)
Clinical signs in the heart preceding electrocardiogram	No case	1 (3 %)	5 (6 %)
No clinical or electrocardiographic abnormality	5 cases (20 %)	5 (14 %)	1 (2 %)

The relationship between the state of the heart and the onset of various forms of diphtheritic paralysis is shown by the fact that in forty-one paralytic conditions there was simultaneous deterioration in the myocardium. Only in one-sixth of the cases, however, was this appreciable on clinical examination, whereas the relapse was evident in serial electrocardiograms in one-half of the cases.

It has been shown that the essential feature of electrocardiographic abnormalities in diphtheria is that they are transient. This has been verified by an analysis of about 600 electrocardiograms taken from 100 cases of

diphtheria, most of which recovered. Often, the myocardial damage and affection of the specialized conducting system of the heart is very considerable.

When similar abnormalities occur in the course of chronic inflammatory conditions, e.g. rheumatism or syphilis, a grave prognosis is justifiable. It has been shown by Oppenheimer and Rothschild (4) that such abnormalities arising from non-diphtheritic conditions caused death in half their cases within two years. Such standards of prognosis must be abandoned completely in diphtheria. The records under consideration indicate that there is no degree of myocardial degeneration as recorded by the electrocardiograph which is incompatible with life. There can be no doubt that many patients survive intraventricular block and bundle-branch block. The mortality is much increased, however, when the condition passes on to complete heart-block, but this complication is not by any means invariably fatal.

It is acknowledged that any discussion of circulatory collapse in diphtheria must take into consideration the so-called 'early' and 'late' types of this complication. To differentiate between these two types of circulatory failure, Schwentker and Noel (5) have tabulated the characteristic features of both, the comparison being based upon the pathological work of Warthin (6). Briefly it may be stated that 'early' failure is due to an intense, generalized toxæmia, the effect of which is shared by the myocardium but only to the same extent as in the other organs. In the 'late' type of failure, however, the clinical signs of heart failure are attributed to reparative processes taking place in the heart-muscle and commonly resulting in lesions of the bundle of His and its branches. The authors make it quite clear that this classification is distinct from the conventional idea of 'early' and 'late' circulatory failure so called merely on account of the time of onset of the complication.

As may be expected, the allocation of cases into these two groups is not always easy. In this series of 100 cases, however, seventeen deaths occurred. Two, due to diaphragmatic paralysis, are excluded, but five were classed as typical of 'early' cardiac failure. Case No. 33 may be taken as an illustration of this type:

Boy, aged 5 years. Fifth day of disease on admission. Extensive faucial and nasal membrane. Foetor oris. Markedly toxic. Cyanosis. Heart-sounds well defined. ADS: 112,000 units (part intravenously).

Electrocardiogram No. 1 (on admission). Plate 17, Fig. 19. *Observations*: Rate 144 per min. Action regular. *P-R* 0.1 sec. *QRS* 0.06 sec. Disappearance of iso-electric line between *R* and *T* most marked in Lead II. *T*-waves positive in all leads: early biphasic changes in Lead III. Pointed *P*-wave in Lead III. Tendency to right ventricular preponderance. *Interpretation*: No definite evidence of myocardial or conductive lesions.

Electrocardiogram No. 2. Plate 17, Fig. 20. Sixth day of disease. *Observations*: rate 165 per min. Action regular. *P-R* 0.1 sec. *QRS* 0.08 sec.

T-waves positive in all leads: incomplete descending limb in Lead III. Pointed *P*-waves still present. Right ventricular preponderance more marked. *Interpretation*: Ventricular preponderance may be accounted for by unequal distribution of myocarditis. Conduction time in the Purkinje system is somewhat increased. *Clinical observations*: The general condition of the patient deteriorated steadily and there was no apparent response to specific treatment. Within a few hours of the second electrocardiogram being taken the patient died from circulatory collapse characterized by pallor, cyanosis, rapid thready pulse and low blood-pressure. Before death the heart-sounds became softer and gallop rhythm developed.

It is to be noted that an electrocardiogram was not obtained during the final stage of circulatory failure, yet this case is typical of a small but definite group of cases dying of diphtheria in which there are clinical signs of deterioration in the circulatory system unaccompanied by corresponding abnormality in the heart itself when investigated clinically and by the electrocardiograph. The remaining ten fatal cases in the series showed gross electrocardiographic changes amounting to complete heart-block at some stage of the disease. Such lesions are typical of the 'late' type of circulatory collapse described by Schwentker and Noel (5). When diphtheritic toxæmia is so severe that degeneration in the heart results in complete auriculo-ventricular dissociation, the prognosis is extremely grave. This is in agreement with Stecher's observations (1) on the subject, and Harding's to the effect that heart-block is 'almost invariably fatal'.

There is no doubt, however, that cases of this kind recover: such a case, for example, is described by Ducamp and Janbon (7). In Chamberlain's case (8) complete heart-block developed during diphtheria, and not only did the patient survive, but the cardiac defect remained as a permanent condition. In two cases of the present series complete heart-block was a transitory complication followed by death from causes other than cardiac failure. It remains to be pointed out that complete heart-block in diphtheria is often particularly difficult to diagnose by clinical methods alone because the ventricular rate is often about 100 per minute. Owing to this fact there can be little doubt that the frequency of this complication is underestimated. In support of this contention it may be mentioned that in only two hospitals for infectious diseases in this country is the electrocardiograph used. Very occasionally one sees a patient who tolerates the onset of complete heart-block with comparatively little change in his general condition, but as a rule there are signs of grave circulatory disturbance such as pallor, vomiting, tachycardia or bradycardia, hypotension, and restlessness. The writer believes that in the 'late' type of circulatory failure in diphtheria, in which complete heart-block is commonly found, this deterioration of the peripheral circulatory system is of primary importance in the fatal termination of the disease.

It is possible that failure may be of purely mechanical origin. Thus, a collapsed peripheral circulation may, at a given time, be sufficient to sustain the vital centres of the brain in spite of a damaged and badly func-

tioning myocardium, but the sudden onset of complete heart-block reduces the cardiac function so rapidly that syncope occurs soon after the onset of the conductive lesion.

Another mechanism suggests itself as a possible explanation of circulatory failure in diphtheria. It has been shown in the series of cases that many forms of diphtheritic paralysis are often accompanied by a relapse in the condition of the heart. It is very likely, therefore, that when a cardiac lesion occurs there is an exacerbation of degenerative changes elsewhere, including the medullary centres in the brain. Furthermore, as suggested previously, the decreased efficiency of the heart is likely to contribute to this effect.

It is not the writer's intention to embark on any new theory in an attempt to explain circulatory collapse in diphtheria. What has been written is largely an attempt to look at the problem from the point of view of electrocardiography. To some extent the result of the work is negative in value, inasmuch as the conclusion is reached that changes in the heart alone are insufficient to account for death. The writer believes that in 'early' circulatory collapse the heart lesion is of secondary importance and often may not enter into the picture to any appreciable extent, and in the 'late' cases of death, though the heart lesion is gross and probably contributes to the fatal ending, there is yet another factor concerned. Work has recently been done in the Birmingham City Hospital on the carbohydrate metabolism in diphtheria in an effort to investigate changes in nutrition which accompany severe toxæmia in this disease. The results of these investigations are described elsewhere (9, 10), but it may be stated here that one of the general conclusions is that circulatory disturbances in diphtheria are largely due to a derangement of carbohydrate metabolism through which all the body tissues are affected.

Conclusions

1. The electrocardiograph is a valuable means of estimating the severity of diphtheritic myocarditis and the only means of accurate diagnosis of conductive lesions in the majority of cases.

2. Though a large proportion of cases having mild myocarditis are undetected by clinical methods, such cases become comparatively rare in the moderate and severe types of diphtheria. Hence for practical purposes the character of the heart-sounds is usually a sufficiently accurate guide to the state of the myocardium.

3. The clinical signs which are most closely related to the electrocardiographic findings are those dependent on cardiac function, e.g. response to effort and the trend of the pulse-rate. The significance of persistently 'abnormal' heart-sounds can be safely estimated by the electrocardiogram and the patient's response to effort, considered together.

4. Of the various physical signs in the heart taken to indicate myocarditis in diphtheria, the most valuable as confirmed by simultaneous electrocardiographic records are: (a) progressive softening of the first heart-sound at all

areas, especially the mitral and aortic areas. (b) The character of the cardiac impulse at the apex and movement of the apex-beat to a position farther away from the midline. (c) Splitting of the first mitral sound producing a triple rhythm.

5. Serial electrocardiographic records show that with the onset of diphtheritic paralyses there is, in a considerable proportion of cases, a simultaneous relapse in the condition of the heart. This fact is much less frequently observed when clinical methods alone are employed.

6. The severity of the cardiac lesion is usually proportional to the severity of the toxæmia when specific treatment is commenced. There are, however, cases in which neither the clinical nor the electrocardiographic abnormalities are sufficient to account for the state of impending circulatory collapse which is often seen in diphtheria.

7. Although gross degeneration of the heart-muscle and specialized conducting system are frequently shown by the electrocardiograph during diphtheria, these lesions are mostly transient. Complete heart-block is by far the commonest lesion associated with circulatory collapse ending fatally, but complete block is probably only a contributory factor in a condition characterized by widespread changes in the circulatory system.

8. Fifteen fatal cases are classified according to the 'early' and 'late' types described by Schwentker and Noel. Except in the event of complete heart-block, no reliance can be placed upon the electrocardiographic findings in diphtheria in assessing prognosis.

Dr. E. C. Benn and Dr. Violet H. Comber obtained most of the records in previous years, and the writer has also had valuable assistance from Professor K. Douglas Wilkinson in the interpretation of some of the electrocardiograms.

I am indebted to Dr. E. H. R. Harries, the Medical Superintendent of the Birmingham City Hospital, for permission to publish this paper, and to Professor G. Haswell Wilson for pathological reports on serial sections of the bundle of His in a number of fatal cases.

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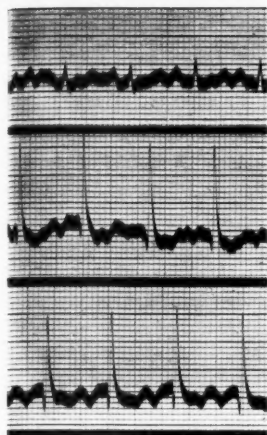


FIG. 1

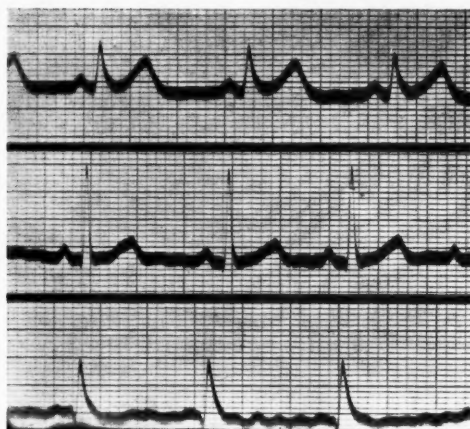


FIG. 2

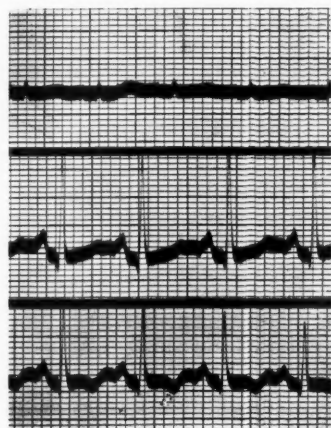


FIG. 3

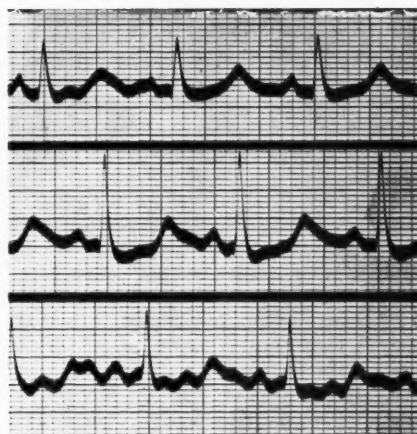


FIG. 4

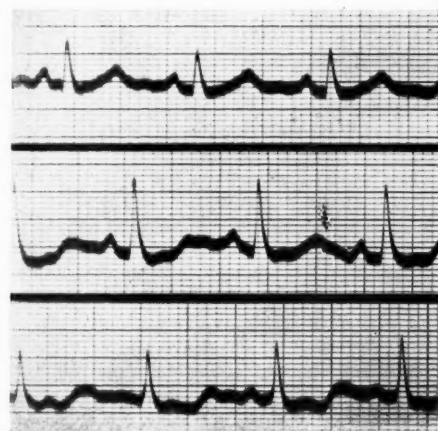


FIG. 5

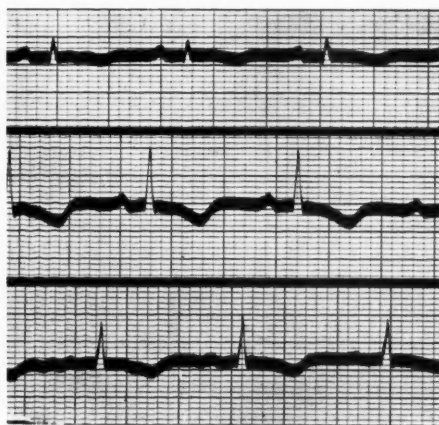


FIG. 6

Fig. 1: Case 5, *Electrocardiogram 1*, Tachycardia associated with a moderate degree of myocarditis. Fig. 2: Case 32, *Electrocardiogram 6*, Fairly advanced degree of myocarditis and slight delay in intraventricular conduction. Fig. 3: Case 41, *Electrocardiogram 1*, Suggests onset of myocardial changes, but may be normal for the individual. Fig. 4: Case 41, *Electrocardiogram 3*, Myocarditis established. Fig. 5: Case 41, *Electrocardiogram 5*, Myocarditis increasing. Fig. 6: Case 41, *Electrocardiogram 12*, Considerable myocardial damage

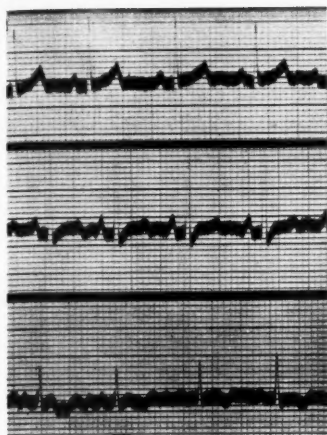


FIG. 7

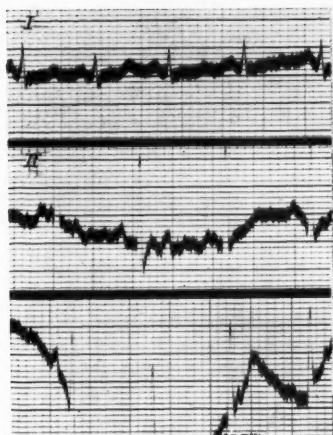


FIG. 8

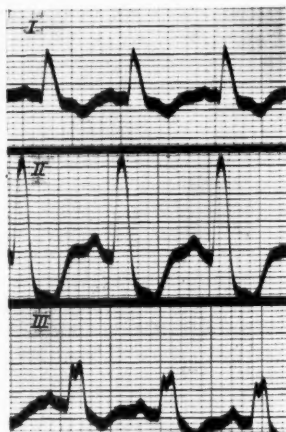


FIG. 9

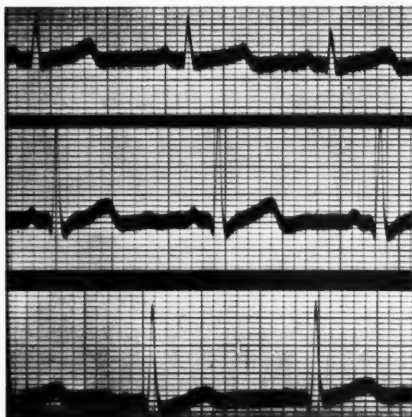


FIG. 10

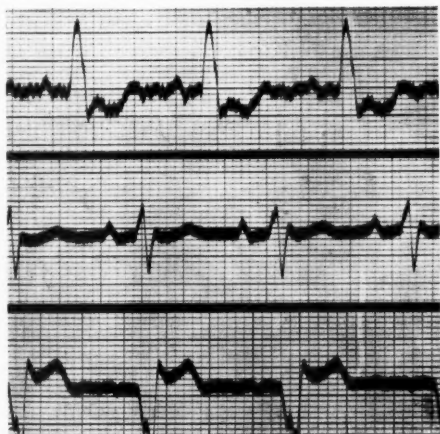


FIG. 11

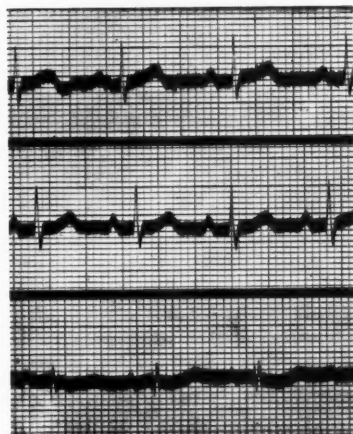


FIG. 12

Fig. 7: Case 41, Electrocardiogram 14, Electrocardiographic recovery. Fig. 8: Case 101, Electrocardiogram 1, Except for tachycardia the record is normal. Fig. 9: Case 101, Electrocardiogram 4, Delayed conductivity in the walls of the ventricles associated with a considerable degree of myocardial damage. Fig. 10: Case 101, Electrocardiogram 15, Advanced convalescence. Fig. 11: Case 27, Electrocardiogram 1, Right bundle branch block. Alternation of the bundles seen in Lead 1. Fig. 12: Case 27, Electrocardiogram 16, Normal record in advanced convalescence

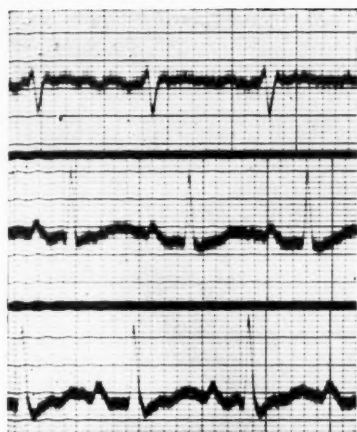


FIG. 13

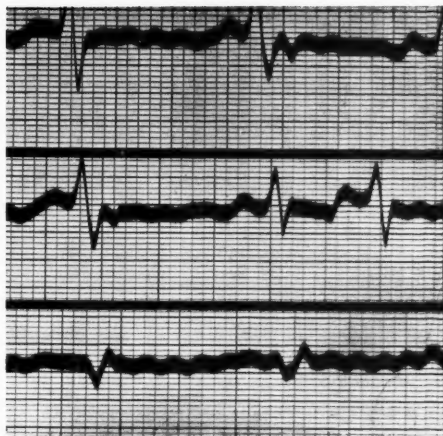


FIG. 14

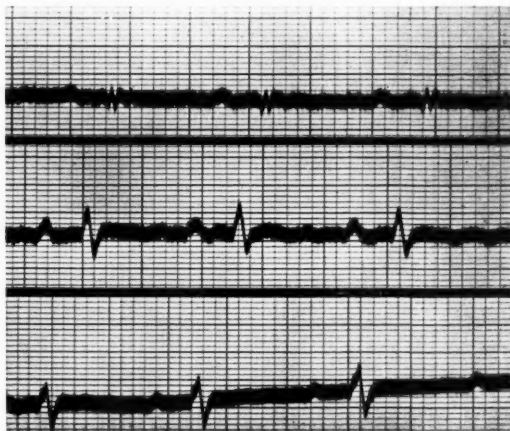


FIG. 15

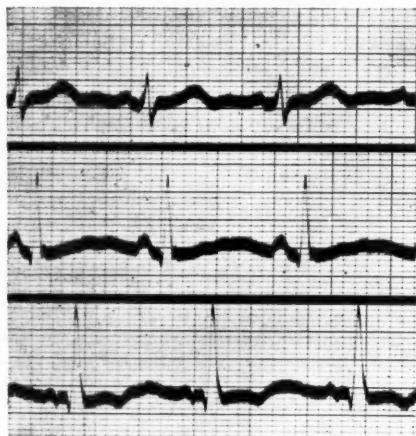


FIG. 16

Fig. 13: Case 102, *Electrocardiogram 1*, Record is within normal limits except for tachycardia.
 Fig. 14: Case 102, *Electrocardiogram 6*, Complete heart-block. Fig. 15: Case 102, *Electrocardiogram 10*, Auriculo-ventricular relationship re-established; slight delay in conduction time from auricle to ventricle, but P.R. is within normal limits. Fig. 16: Case 103, *Electrocardiogram 1*, Record is within normal limits, but suggests onset of myocardial damage



FIG. 17

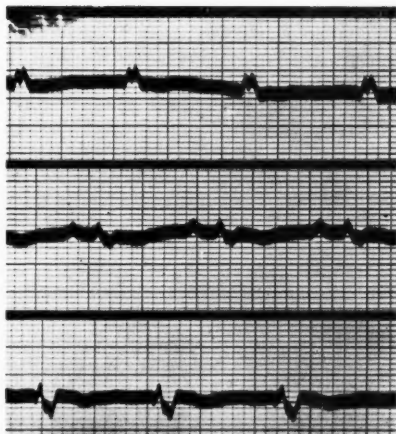


FIG. 18

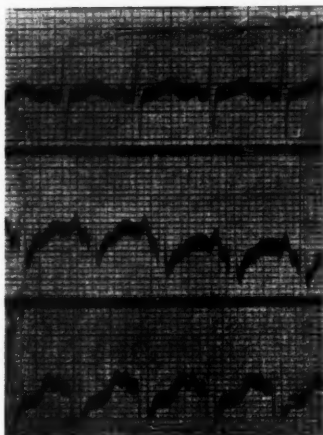


FIG. 19

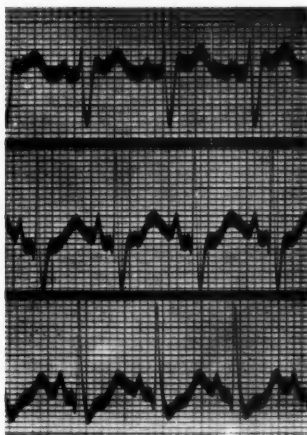


FIG. 20

Fig. 17: Case 103, Electrocardiogram 3, Complete heart-block. Fig. 18: Case 103, Electrocardiogram 9, Considerable myocardial damage, but auriculo-ventricular conduction re-established. Slight intraventricular delay. Fig. 19: Case 33, Electrocardiogram 1, No definite evidence of myocardial or conductive lesions. Fig. 20: Case 33, Electrocardiogram 2, Ventricular preponderance may be due to unequal distribution of myocarditis. Conduction time in the ventricle is somewhat increased

A STUDY OF THE TOTAL EXCHANGE OF WATER, SODIUM, POTASSIUM, AND NITROGEN IN EPILEPSY¹

By F. B. BYROM²

(From the Department of Medicine, the University of Chicago)

With Plates 18 and 19

RECENT research in epilepsy has indicated that the incidence of convulsions may be modified, favourably and otherwise, by changes in the balance of water and electrolytes in the body fluids. In a significant proportion of cases, especially amongst children, measures which deplete the alkali reserve of the body, such as starvation (11), artificially induced ketosis (29), ingestion of acid-forming salts such as ammonium chloride (15), and rebreathing of expired air (16) either relieve or abolish fits. On the other hand, alkalosis, induced by administration of sodium bicarbonate (17) or by overbreathing (24, 7), will often precipitate convulsions in epileptic subjects.

There is, however, no convincing evidence that the fit is a simple function of the pH of the body fluid. Alkalosis does not cause convulsions in subjects not liable to epilepsy, and the clinical results of acid therapy in epilepsy do not tally very closely with the changes actually observed in the acid-base balance of the blood. The acidosis provoked by a ketogenic diet, for example, is a transient phenomenon (15), yet the beneficial effect, if any be obtained, persists as long as ketosis, as distinct from acidosis, is maintained.

The attempt to find a more adequate explanation of these facts has diverted the attention of more recent workers towards the study of water balance, a wider and more fundamental phase of metabolism which, while intimately dependent on acid-base equilibrium, is also sensitive to other influences.

The current conception of the relation between electrolyte and water equilibrium rests mainly on the work of Gamble and his associates (10) and may be stated in the following terms: The excretion of water, on the one hand, and of fixed alkaline base on the other, is so ordered that the concentration of these bases in the several body fluids is maintained at a constant level. Any rise or fall in the total level of base in the body will entail a proportionate gain or loss of water and vice versa. Furthermore,

¹ Received November 23, 1931.

² The experiments to be described formed the basis of a paper read, in conjunction with Professor Russell M. Wilder, before the Annual Meeting of the Society for Clinical Investigation at Atlantic City, New Jersey, on May 4, 1931.

[Q.J.M. New Series No. 2]

since potassium is confined almost exclusively to the cell, and sodium to the fluid surrounding the cell, changes in the total exchange of these separate bases may be interpreted as indicating corresponding movements of cellular and interstitial fluid respectively.

It has been shown by Gamble, Blackfan, and Hamilton (8) that acidosis induced by ammonium chloride leads to an extrusion of water and fixed base in amounts which are in agreement with the above premisses. It is uncertain whether the primary effect of such acidosis is exerted on base or water balance. There is no *a priori* reason why acidosis should cause a primary loss of fixed base, for the kidneys are able to furnish from urea enough ammonia to balance the excess acid radicles during excretion. Unless, therefore, a lag in mobilization of the urea-ammonia factor be postulated, the alternative explanation, namely, that acidosis leads to an initial loss of water, with secondary adjustment of base balance, must be considered equally possible.

Whichever view should prove to be correct, the association between acid-base and water equilibrium has led to the suggestion that the benefit derived from acid therapy in epilepsy may be attributable to the dehydration to which it gives rise. If so, it follows that other methods of provoking dehydration should be equally successful. This possibility has been explored, independently, by McQuarrie (19) and Fay (6), both of whom have reported favourable results from extreme limitation of fluid intake. Pursuing the problem farther, McQuarrie has shown that the ingestion of large quantities of water will precipitate convulsions in epileptic children, especially if at the same time diuresis be postponed by injections of pituitrin. In one instance this procedure led to status epilepticus, but the convulsions promptly ceased after diuresis had been promoted by means of urea.

There can be no question, then, that artificial alterations of water balance modify the incidence of epileptic convulsions. It does not follow, however, that epilepsy is simply an expression of disturbed water balance, analogous to the convulsions which Larson, Weir, and Rowntree (14) induced in animals by forced administration of water. Before such an hypothesis can be entertained it must be shown that, in the ordinary course of the disease, the convulsions are preceded by spontaneous retention of water. This criterion has not yet been satisfied. Gamble and Hamilton (9), however, observed that in epileptic children the excretion of sodium rose considerably during periods of convulsions and, for the reasons outlined above, they interpret this change as indicating a loss of extracellular water *during* the convulsion. They were unable to decide whether or not this loss was simply a result of the fit.

With the object of defining more clearly the role of water and electrolyte balance in the aetiology of epilepsy it was decided, in the present research, to undertake daily measurements of the total exchange of water, sodium, potassium, and nitrogen in epileptic subjects during the various phases of the disease, on normal and on ketogenic diets.

Experimental Methods

The patients were kept under close observation in separate rooms, and care was taken to minimize sweating and exposure to cold. They were sponged daily with tepid water, baths being forbidden. Throughout the experiments the fluid intake was neither restricted nor regulated, but the intake of protein, fat, and minerals was held constant. Daily measurements began and ended at 8 a.m., after the patients had voided excreta, but before food or fluid had been taken. The body-weight was determined at this time on special 'silk' scales, sensitive to increments of 5 gm.

Water balance. The determination of total exchange of water involves measurement of the following fractions.³

- Water gained.* (1) Water drunk.
 (2) Water contained in solid foods.
 (3) Water liberated during the catabolism of protein, fat, and carbohydrate (water of combustion).

- Water lost.* (4) Urine water.
 (5) Faeces water.
 (6) Water lost insensibly through the skin and lungs.

The measurement of fractions (1), (2), (4), and (5) presents no serious difficulty. Urine water has been calculated from volume and specific gravity readings, and food water from the loss of weight sustained by 50 per cent. aliquot portions of the diets served, after drying in a current of hot air at 60°C., the residue being then ground and desiccated to constant weight over sulphuric acid.⁴ Faeces water has been determined in the same way. Precautions have been taken to avoid, as far as possible, loss of water by evaporation from the food served.

Fractions (3) and (6) cannot unfortunately be measured directly, since they entail an estimate of the total amounts of protein, fat, and carbohydrate burnt. This, the metabolic mixture, has been determined in the following way, as suggested by Johnston and Newburgh (13). Benedict and Root (3) have shown that when sweating, exposure to cold, and muscular work are excluded, the total caloric output is a linear function of the insensible loss of weight, that is, the loss due to escape of water and carbon dioxide through the skin and lungs, less the oxygen absorbed. The insensible loss of weight over a given period can be determined from the observed gain or loss of body-weight, if the weights of fluid and food ingested and of faeces and urine voided are known. From the total caloric output so determined the calories derived from protein breakdown (urine nitrogen \times 26.51) have been subtracted and the remaining calories have been divided between fat and carbohydrate by means of an arbitrary respiratory quotient. With a carbohydrate intake of 100 gm. per diem a respiratory quotient of 0.82 has been presumed, but on lower carbohydrate intakes it has been assumed that the whole of the carbohydrate ingested has been oxidized, the remaining non-protein calories being derived from combustion of fat. Given that

³ Some workers include in the balance water liberated from physical combination with body protein when the amount of the latter catabolized exceeds that furnished by the diet. Since such water is already present in the body as H_2O , this procedure seems unnecessary.

⁴ Foods rich in fat such as butter and mayonnaise were desiccated separately.

1 grm. of carbohydrate, fat, and protein produce, during combustion, respectively 0.55, 1.10, and 0.43 grm. of water, the water of combustion (fraction (3)) can now be calculated. The remaining fraction (6) has been estimated from the insensible loss of weight by applying corrections (derived from the above data) for the carbon dioxide and oxygen exchange. The tedious arithmetical processes involved in the determination of water balance by the above method are fully described by Newburgh, Johnston, and Falcon-Lesses (21).

Criticism

The validity of the assumptions on which the above method of determining water balance rests is affected by muscular work and sweating, neither of which can be prevented during epileptic convulsions, and also by the presence of ketosis. As a means of studying the separate behaviour of the various component fractions of the balance, however, the procedure is necessary and the experimental error, though considerable, is small enough to permit qualitative conclusions. Expressed in terms of the net daily balance, however, the possible error assumes more serious proportions. In practice it has been found that the daily water balance has agreed as a rule with the change in body-weight to within 50 grm., but on occasional days the discrepancy has amounted to 100 grm. or more. In experiments of this nature where the caloric intake is adequate there can be little doubt that the body-weight, determined under the conditions described, furnishes an equally satisfactory measure of the net water exchange.

A third estimate of water balance has been derived, by calculation, from the total exchange of sodium and potassium, accepting the principles of Gamble, described above, and using the equations of Peters and Van Slyke (22). The escape of mineral, especially sodium, unmeasured through the skin inevitably lends to this estimate a positive bias, which is most noticeable on those days (Figs. 1 and 2) on which the abnormally high values for 'insensibly' lost water indicate that sweating has occurred. With these exceptions, however, it is evident from Plate 18, Fig. 4 and Plate 19, Fig. 5, that the three separate estimates of water balance (recorded on the same scale) are in rough qualitative agreement.

Mineral and Nitrogen Analyses

Sodium has been determined gravimetrically in combination with uranyl zinc acetate (1); potassium by conversion into iodoplatinate and microtitration with sodium thiosulphate (26); and nitrogen by Kjeldahl's method. The data for food are based on analysis of 50 per cent. aliquot portions of the diets served (in Case 1, one day; in Case 2, average of five days). A constant correction has been applied in each case for faecal loss (Case 1, N average of six days, Na and K average of nineteen days; Case 2, N average of fifteen days; Na and K average of nine days). The final balances of sodium and potassium have been charted, on the same scale, in milligramme-molecular equivalents (Plate 18, Fig. 4 and Plate 19, Fig. 5).

Experimental Results

Case 1. In this patient the presence of progressive gigantism, the occurrence of upward rotation of the eyeballs during convulsions, and the history of a period of excessive thirst (the last symptom may, of course, have been merely physiological) are circumstances suggesting disease of the neurohypophyseal mechanism, a region of the nervous system known to exert an influence on water metabolism. The patient therefore seemed a particularly suitable subject for an investigation of the supposed relation between water balance and epilepsy.

Effect of ketogenic diet. In the first eight days of the period of ketosis there occurred a progressive loss of weight, water and sodium (Plate 18, Fig. 4). The potassium balance remaining relatively in equilibrium, it is clear that the lost fluid has been derived from extracellular sources. It has been recognized since the experiments of Stark (27) that considerable changes in fluid balance occur when the carbohydrate intake is altered. Benedict and Milner (2), using direct methods, observed that a change from a high carbohydrate diet to one rich in fat (but not ketogenic) led to an immediate and gross loss of water. This change has never been satisfactorily explained. Bridge and Bridges (5) point out that it is not due to the liberation of water from physical combination with glycogen. In the present experiments, however, it is not unreasonable to associate the dehydration with the presence of ketone acidosis. The loss of water in the cases studied is circumscribed and does not exceed one or two kilogrammes, and after a few days the fluid balance of the body re-enters equilibrium at a lower absolute level. It is doubtful if this low level of hydration is maintained indefinitely in the presence of ketosis. Clinical experience indicates that the lost weight is eventually regained, and Hastings, Liu, and Dieuaide (12) have found that the dehydration induced by ammonium chloride acidosis is only of brief duration. It seems not unlikely, therefore, that the ammonia factor of the kidneys not only checks the dehydration, but also permits the eventual re-accumulation of some, if not all, of the lost salt and water.

Nitrogen balance. As soon as the diet is made ketogenic the nitrogen excretion mounts rapidly for several days, exceeding the intake by a considerable margin, and subsequently falls more gradually until equilibrium is restored. The loss of nitrogen is too great to be accounted for by the washing out of non-protein nitrogen during dehydration (23) and therefore indicates destruction of preformed protein.

The body protein may be divided into three main fractions: first, that which forms an integral part of living protoplasm—the gradual replacement of which can be gauged by the excretion of creatinine; secondly, a more readily mobilized reserve, 'deposit protein' (18, 4), maintained by the cell to meet current debts without encroachment on its structural capital; and, thirdly, extracellular protein, which may be considered to be confined to the blood-plasma. In the present instance the excess nitrogen can hardly have been derived from plasma protein, for the amount of nitrogen lost represents the protein content of approximately a litre of plasma. Further, the unchanged creatinine excretion indicates that no undue destruction of cell protoplasm has occurred, so that the brunt of the loss must have been borne by intracellular-deposit protein. It is widely believed that the protein of the body holds about four times its weight of water in physical combination, and that destruction of the former leads to elimination of the latter. During

the period under discussion (i.e. from the 11th to the 16th day of the experiment), however, the potassium balance suggests that no water has left the cells. Moreover, during a later period (from the 22nd to 26th day) a further loss of protein occurs at a time when potassium is being actively retained. These circumstances suggest that the combustion of intracellular protein does not necessarily entail the discharge of water or, at least, of potassium from the cell.

That restriction of carbohydrate intake leads to an increased demand for protein is a well-known fact, but the temporary nature of this dislocation of nitrogen balance is not so widely realized and is of some practical importance. The immediate effect of a ketogenic diet on nitrogen excretion has been cited by Talbot (28) in support of his contention that patients on such diets require increased allowances of protein. Without attempting to decide this disputed question it is obvious that the nitrogen balance must be observed for at least several weeks before such conclusions can be accepted.

Changes in metabolism in relation to convulsions. The changes in metabolism during convulsions are well illustrated by the two attacks which occurred on the 19th day of the experiment (Plate 18, Fig. 4). Both convulsions took place during the night, shortly before the period of collection ended, before any substantial readjustment was possible. A third convulsion followed at 11.30 a.m., that is, within the first four hours of the 20th daily period.

Water and sodium. There is a sharp loss of body-weight, water, and sodium, changes which fulfil the prediction of Gamble and Hamilton, previously referred to, that the convulsion is accompanied by a discharge of extracellular body fluid, and also recall the old clinical observation that fits are often followed by polyuria (Fig. 1). The determined loss of water (1,060 grm.), which agrees closely with the fall in body-weight (1,050 grm.) is greatly in excess of the loss predicted from the mineral exchange (320 grm.). It is unlikely that this discrepancy is due to loss of sodium in sweat, for the amount of water perspired on that day (Fig. 1) is not significantly higher than during the preceding eight days, when the determined (1,580 grm.) and the predicted (1,420 grm.) water losses are in much closer agreement. Admitting the danger of drawing quantitative conclusions from such data, there is at least a suggestion that the primary change attendant on the convulsion is a loss of water, and that the loss of sodium is a secondary and somewhat later adjustment.

The compensatory reaction which follows this dehydration is more than sufficient to restore fluid equilibrium. The body-weight returns to, and then exceeds, the preconvulsive level, and for a period of seven days there is retention of water and sodium. The significance of these fluctuations in fluid balance is obscure. During the convulsion excessive production of lactic acid combines with respiratory embarrassment to cause considerable temporary acidosis.⁵ This acidosis may be partly, but is not wholly, responsible. The extra sodium excreted is balanced, not by organic acid but by chlorine; and a similar, though less marked, loss of salt and water has been observed by Gamble and Hamilton (*loc. cit.*) during a period of petit mal, when lactic acidosis was presumably absent.

Potassium. The convulsions which occurred on the 19th and 20th days

⁵ In Case 3, blood was taken from a finger during a severe convulsion and examined by the micro-technique of Shock and Hastings (25). The plasma pH had fallen to 7.13 (normal limits 7.35-7.45) and the bicarbonate to 10 milli-equivalents per litre (normal limits 22-28).

(and on other occasions) are accompanied by little or no loss of potassium.⁶ On the following (21st) day, however, the balance enters a positive phase which persists for several days after sodium and water equilibrium has been regained. Possibly the need for water and base at this time is so urgent that the body no longer discriminates between sodium and potassium.

Nitrogen. The minor and inconstant changes in nitrogen balance during and after convulsions no doubt represent the effect of sudden excursions in water balance on the elimination of non-protein nitrogen.

All the changes described above accompany or follow the convulsions. There is no evidence of disturbance of water or mineral balance in the pre-convulsive phase. The convulsions on the 19th day occurred after a period of dehydration lasting eight days. They caused, in turn, a further loss of a kilogramme of water, yet a third attack occurred within four hours. Moreover, considerable retention of water ensued in the following four days without provoking any further convulsions. *A negative water balance, therefore, does not necessarily prevent, nor does a positive balance necessarily induce, convulsions.* It is also evident from Fig. 1 that an increased water intake does not necessarily precede the spontaneous convulsions. The water intake rose sharply on the 20th day, but this may be regarded as a response to the dehydration provoked by the two convulsions which occurred during the previous night.

Case 2. In this patient the intervals which elapsed between groups of convulsions were relatively short, and retention of water is apparent in the days immediately preceding the latter (Plate 19, Fig. 5). In the light of the results obtained in the first case, it is obvious that this chain of events must be regarded as sequence rather than consequence. In the main the changes observed (Plate 19, Figs. 5 and 2) corroborate those found in the previous case. There is a parallel loss of weight, water, and sodium during the period of ketosis, punctuated by the fluctuations accompanying the convulsions. The nitrogen balance also shows the same tendency, after the initial dislocation, to return towards equilibrium, and does not bear any close comparison with the potassium balance.

Unlike the first case, however, this patient had been restricted to a low salt diet (0.7 gm. Na daily) for the three weeks immediately preceding the experiment and had lost about 2 kilogrammes of weight in this period. This previous depletion of the interstitial-fluid reservoirs no doubt explains the relatively small loss observed during the period of ketosis. The case also differs in that the positive potassium balance recorded during the preliminary control period gradually diminished after ketosis appeared. This, again, may have been due to paucity of available sodium.

Case 3. Incontinence of urine during convulsions, and the onset of menstruation, led to the abandonment of detailed water-balance measurements early in this experiment, but the body-weight (Fig. 3) may be regarded as an index of the level of body fluid. The daily salt intake was inadvertently increased by about 7 gm. in changing from the normal to the high fat (non-ketogenic) diet on the 8th day, an error which accounts for the sudden increase in weight at this time. From this day onwards the salt content of the diet was held approximately constant and it will be observed that, as in the

⁶ It must be remembered that small quantities of potassium are present in extracellular water.

previous two cases, the ketogenic diet caused a rapid loss of water, the curves of body-weight and of plasma bicarbonate pursuing roughly parallel courses. Neither the retention of water caused by the increased salt intake nor the dehydration accompanying the ketosis appear to have altered the sequence of convulsions in any way.

Discussion

The observations described above fail to show that spontaneous epileptic convulsions are preceded by any alterations in the total daily exchange of water, sodium, potassium, or nitrogen. They indicate, moreover, that convulsions may occur at a low level, and yet be absent at a relatively higher level, of tissue hydration. It has already been pointed out that epilepsy cannot be regarded as a direct expression of disturbed acid-base balance. It seems equally clear that the convulsion is not a simple function of the degree of hydration of the tissues. At first sight this conclusion appears to conflict with McQuarrie's observation that water retention, induced by increased consumption of water and injections of pituitrin will precipitate convulsions. Pituitrin, however, while postponing the excretion of water, does not hinder the elimination of electrolytes. Consequently, unless the extra fluid administered contains salt, pituitrin will not only augment but will also dilute the body fluids. In later experiments, indeed, McQuarrie (20) has found that, when saline is substituted for water, no convulsions follow although the extra fluid is retained. It is clear, then, that the pernicious effect of antidiuretic measures in epilepsy is referable not to the actual change in bulk of body fluid but to some secondary derangement of water-electrolyte balance. In simpler words, *body water* must not be confused with *body fluid*.

With this distinction in mind, it is difficult to account for the benefit derived from dehydrating measures such as fluid limitation and ketogenic diets. The present observations have shown that the lost water takes with it an equivalent amount of base, and there is no indication that the intrinsic balance between the water and electrolytes of the extracellular body fluid has been upset.

Further research is clearly necessary. The changes in fluid balance attendant upon the convulsion, although probably secondary phenomena, may possess some aetiological significance. It is not known whether they are peculiar to 'idiopathic' epilepsy or whether they can be reproduced in animals by the use of specific convulsant drugs. Closer examination may also show that the epileptic convulsion is preceded by spontaneous local shifts of water or electrolytes across the cell membrane, which are not reflected in the total exchange. The evidence at present available, however, warrants a more conservative conclusion; namely, that the complex equilibrium between water and the various electrolytes of the fluids within or around the neurone may determine the threshold of its response to convulsant agents in general.

Summary

A ketogenic diet causes an immediate circumscribed depletion of the extracellular fluid reserves (water and sodium); a less constant and less marked loss of intracellular fluid (water and potassium); and a temporary draft on the mobile protein reserves of the body.

Spontaneous epileptic convulsions are preceded by no changes, capable of detection in twenty-four hourly measurements, in the total exchange of sodium, potassium, or nitrogen, in the net water balance, or in the several fractions of fluid intake and output which compose the net balance.

The convulsion is attended by a loss of body-weight amounting to as much as a kilogramme. Closer analysis shows that this is due to extrusion of extracellular body fluid (confirming Gamble and Hamilton), largely by the kidneys, but also, to a variable extent, by the skin.

This change is succeeded by a reactionary retention of extracellular fluid, and a corresponding rise in weight. The first change does not necessarily prevent, nor does the second necessarily precipitate, further convulsions.

It is concluded that the epileptic convulsion is not directly conditioned by the degree of hydration of the tissues.

The author is greatly indebted to Professor Russell M. Wilder, under whose direction this research was carried out, for his constant interest and advice; to Professor A. B. Hastings and Dr. N. W. Shock for advice relating to the micro-estimation of acid-base balance; to Miss Florence M. Smith for management of the dietetic details; and to Dr. Lilian Eichelberger and her technicians for nitrogen analyses. The research was undertaken during the tenure of a Fellowship of the Rockefeller Foundation for Medical Research.

Appendix. Case Notes

Case 1. M. K., aged 16, schoolboy.

Diagnosis: Major epilepsy. Gigantism.

Present illness. The patient developed normally until the age of 14, since when he has grown very rapidly. For four months prior to admission he had been subject to severe convulsions, occurring every two or three weeks in groups of three or more. After a short aura—a sensation of numbness in the left foot and ringing in the ears—the eyes rotate upwards, the head becomes tilted backwards, the whole body stiffens, and consciousness is lost. Generalized muscular twitchings follow and the patient finally lapses into deep sleep.

Previous history. Labour was difficult and instruments were used. The patient weighed 7½ lb. at birth. Infancy was uneventful apart from measles and scarlet fever, but when 7 years old the boy fell from a see-saw and was momentarily dazed. He was active and intelligent until a few months ago, since when he has felt weak and depressed. At summer camp, two months before the fits commenced, he complained for several weeks of severe thirst. The convulsions have sometimes been followed by generalized headache, but otherwise there have been no symptoms of increased intracranial tension. There is no family history of epilepsy.

Physical signs. The boy presents the typical features of adolescent gigantism. He is 6 ft. 3 in. tall, symmetrically developed, with no acromegalic stigmata, and has the somewhat querulous attitude characteristic of the pituitary giant. The skull measured 59 cm. in diameter in the occipitofrontal axis. The genitalia are well developed.

Central nervous system. Sense of smell not impaired; optic fundi appear normal; left pupil slightly irregular; both react to light and accommodation; ocular movements full and equal; no ptosis or nystagmus; no facial weakness; tongue protruded in midline; generalized muscular weakness; tendon reflexes symmetrical; abdominal reflexes present and equal; bilateral flexor response to plantar stimulation; no impairment of cutaneous or postural sensation; no ataxia or Rombergism.

Cardiovascular system. Pulse 70–80, regular; apex-beat in 5th intercostal space internal to left mid-clavicular line; heart-sounds normal; no bruits; blood-pressure—systolic 140; diastolic 100 mm. Hg. No evidence of disease of lungs or abdominal organs.

Special investigations. *Perimetry*—no constriction of visual fields; *radio-gram of skull*—no abnormality in sella turcica or elsewhere; optic foramina not constricted; *encephalogram*—ventricles and subarachnoid spaces clearly visualized and free from distortion; *urine*—no abnormal constituents; *sugar tolerance* (after 90 gm. of glucose by mouth)—blood-sugar, fasting 0.08 per cent., 30 minutes 0.151 per cent., 90 minutes 0.100 per cent., 3 hours 0.087 per cent.; *basal metabolic rate* – 22, – 27, – 26; *Wassermann and Kahn reactions*—negative; *blood count*—red corpuscles 6,000,000, leucocytes 7,200 per c.mm., haemoglobin 94 per cent. normal; *electrocardiogram*—normal rhythm.

Case 2. G. D., aged 13, schoolboy.

Diagnosis: Idiopathic epilepsy (major and minor).

Present illness. Transient attacks of loss of memory were first noticed by

the boy's parents three years before admission to hospital. In the last twelve months more severe attacks have supervened. After a preliminary aura—a thumping sensation in the chest—the boy loses consciousness, becomes rigid and cyanosed and develops generalized clonic contractions, afterwards relaxing into a stuporose state. The attacks occur almost every day.

Previous history. Labour was protracted and instruments were used. When 3 years old he was struck in the face by a bicycle and was stunned for a few moments. There is no family history of epilepsy.

Physical signs. A morose, over-nourished boy; no abnormality in optic fundi; no constriction of visual fields; pupils equal, reacting to light and accommodation; ocular movements full and equal; no ptosis or nystagmus; no facial weakness; tongue protruded in midline; no weakness or wasting of limbs; tendon reflexes present and equal; bilateral flexor plantar response; no impairment of postural or cutaneous sensation. No evidence of pulmonary, cardiac, or abdominal disease; blood-pressure—systolic 125, diastolic 80 mm. Hg. No abnormal substances in urine. Radiogram of skull shows no evidence of intracranial tumour.

Case 3. D. D., aged 21, single girl.

Diagnosis: Idiopathic grand mal.

History of present illness. Involuntary contractions of the right hand and arm were noticed at the first onset of menstruation. Shortly afterwards the patient began to suffer from major fits during which she lost consciousness, fell down, and often injured herself. These attacks occurred every few days until 1926 when the patient was confined to a ketogenic diet. Thereafter the attacks were much less frequent until a few months before admission, when she broke diet. There was no previous history of head injury and no relatives are afflicted with epilepsy. Repeated examination has failed to reveal any evidence of organic disease in the nervous system or elsewhere.

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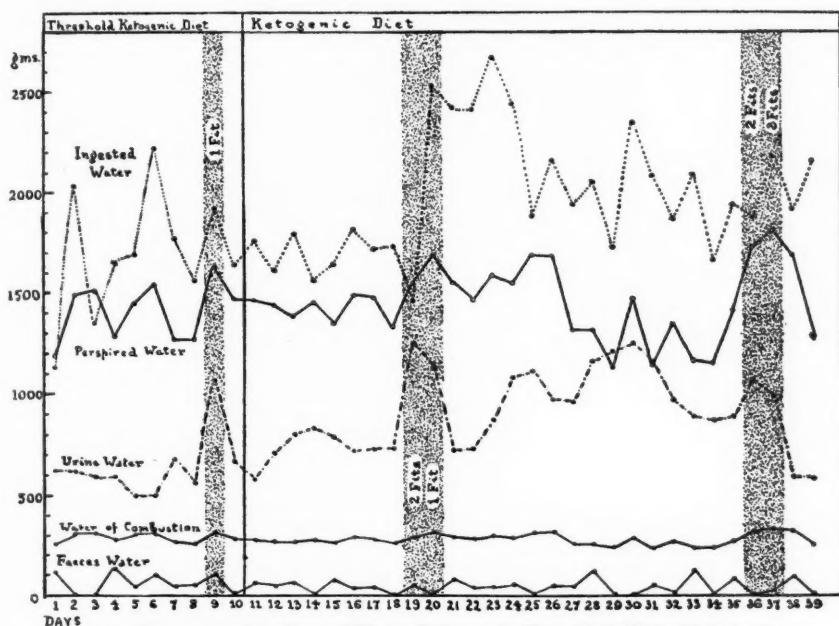


FIG. 1. Component fractions of Water Balance in Case 1 (cf. Plate 18, Fig. 4).

Ingested fluid includes water contained in solid foods. Perspired water includes with the water lost insensibly through the skin and lungs an unknown amount of sensible perspiration.

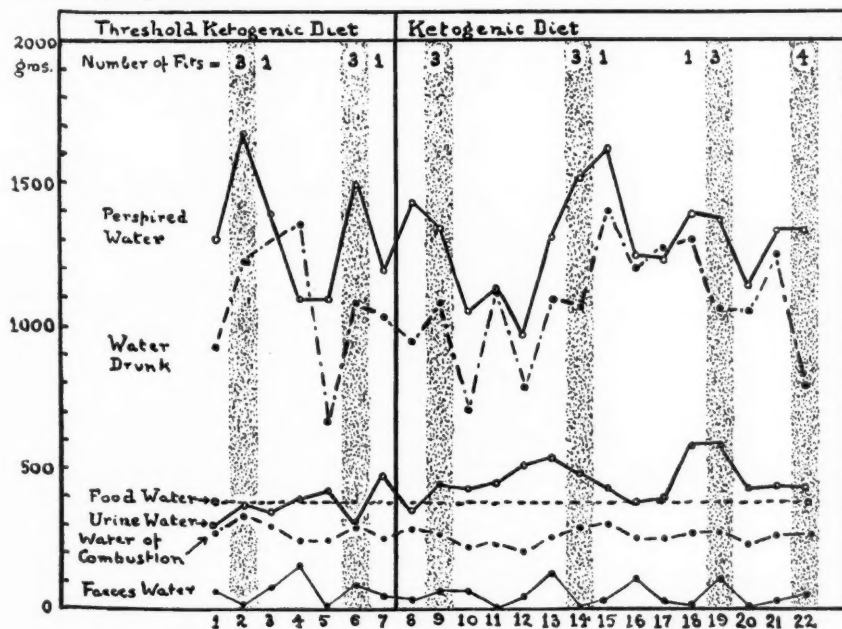


FIG. 2. Component fractions of Total Water Exchange in Case 2 (cf. Plate 19, Fig. 5).

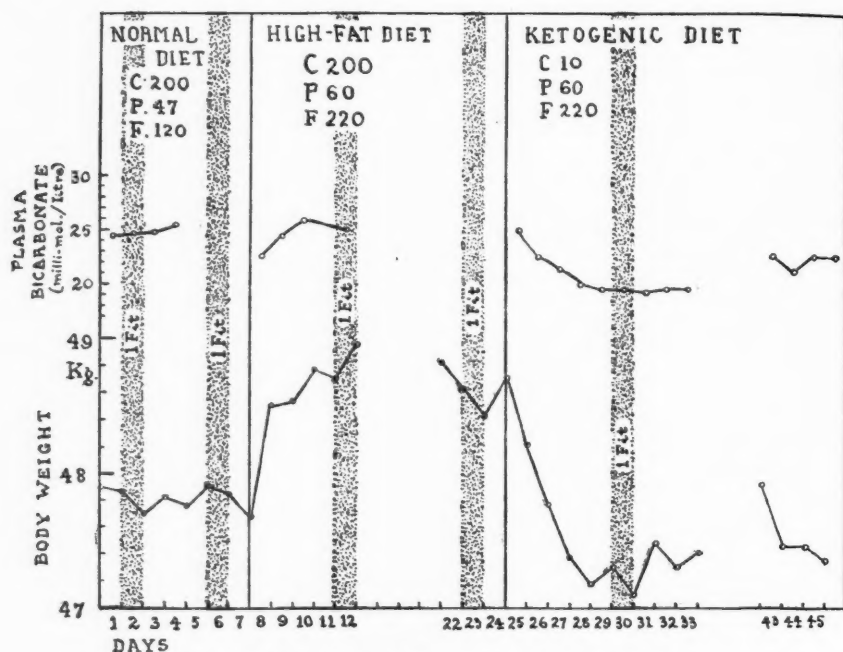


FIG. 3. *Body-weight and Plasma Bicarbonate in Case 3.*

The body-weight may be regarded as an index of the fluid level of the body. Menstruation occurred during the 8th, 9th, and 10th days of the experiment.

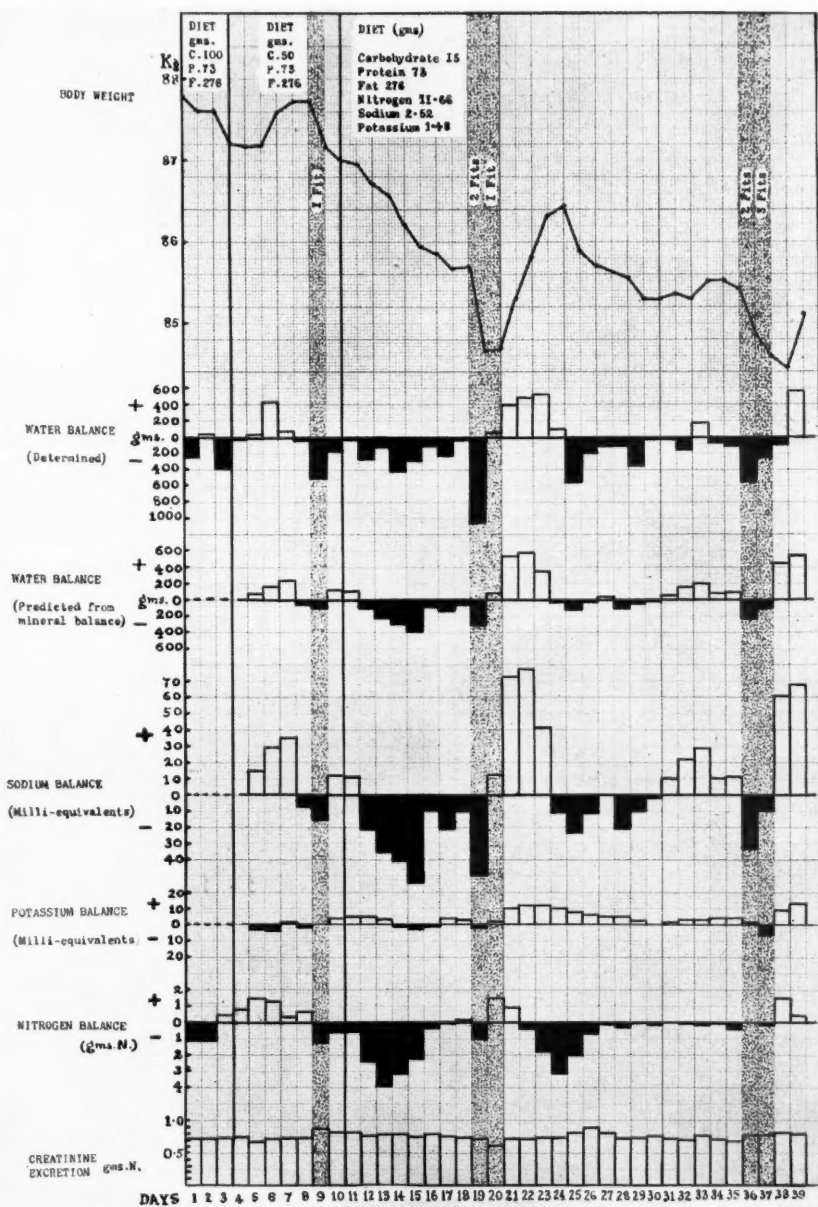


FIG. 4

Metabolism Chart of Case 1. (v. text)

The days on which convulsions occurred are shaded. Ketosis was established by removal of mineral-free cane sugar (candy) from the diet. The urine gave a faintly positive nitroprusside reaction after the fourth day of the experiment; from the eleventh day onwards gross ketonuria was present. The ammonia content of the urine, the data of which have been omitted, increased considerably during the period of ketosis but showed no significant fluctuations in relation to the convulsions

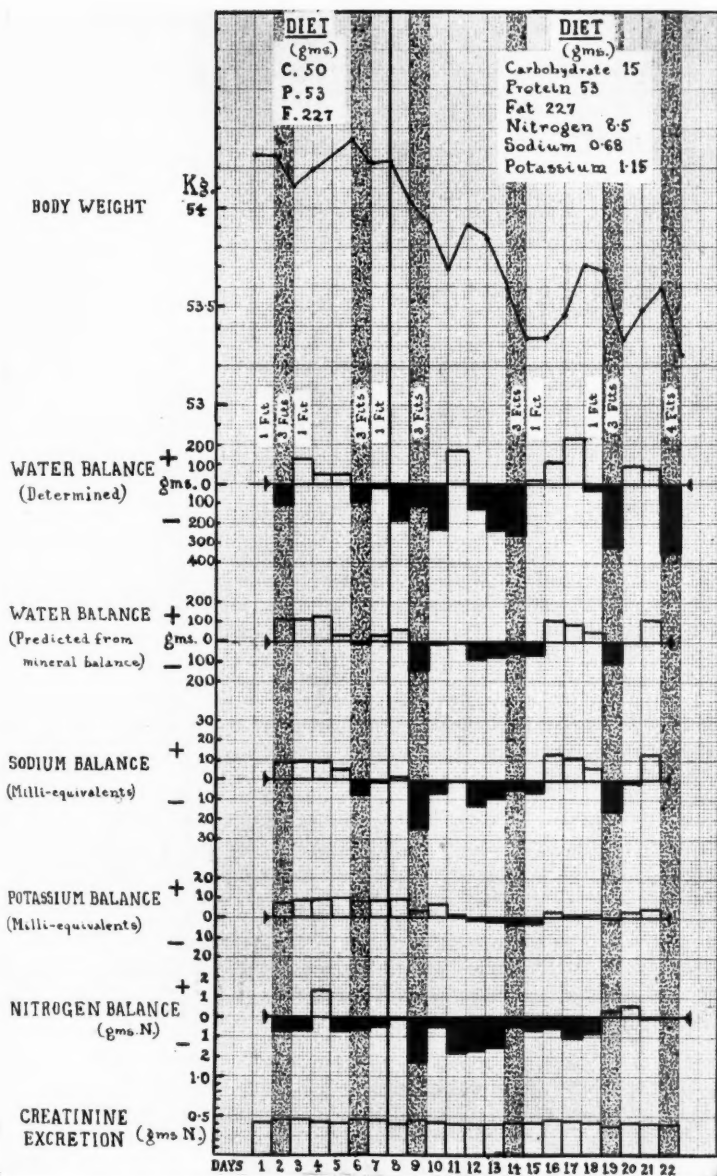
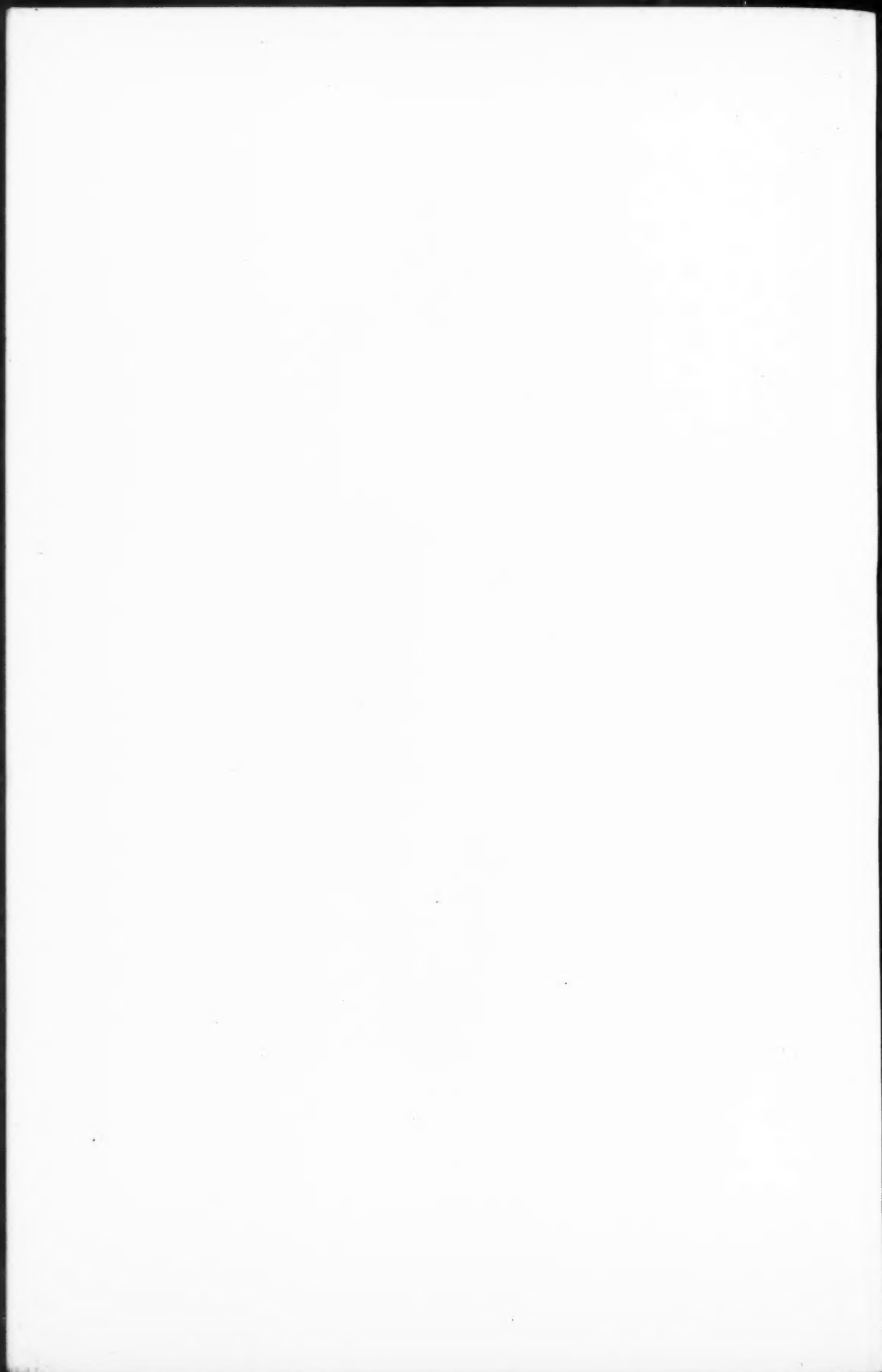


FIG. 5

Metabolism Chart in Case 2

To avoid confusion, only the days on which more than one convulsion occurred have been shaded. The nitroprusside reaction (urine) was faintly positive from the second to the seventh day, and very strongly positive during the remainder of the experiment



UNDULANT FEVER IN THE NORTH-EAST OF SCOTLAND¹

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With Plate 20

ALTHOUGH the aetiological agent of Malta Fever, the *Micrococcus melitensis*, was recognized by Bruce (8) in 1887, as the cause of epidemic abortion in cattle by Bang (4) in 1897, and the cause of a similar disease in pigs by Traum (38) in 1914, it was not until 1918 that the relationship of *Micrococcus melitensis*, *Bacillus abortus* (Bang), and *Bacillus abortus* (Traum) was established by Evans (19). This worker found that the strains of these organisms showed a very close resemblance morphologically, culturally, and serologically, and at that time suggested that *B. abortus* might therefore be the cause of disease in man, although this possibility had also been envisaged by Schroeder and Cotton (32) in 1911.

Since 1918 very numerous investigations have been made into the relationship of *Brucella abortus* to disease processes in man, and these investigations have been particularly exhaustive in the United States and in Denmark. The papers of Kristensen (26), Smith (36), Simpson and Fraizer (34), Dalrymple-Champneys (15, 16), Bulmer (9), Hasseltine (23), Wilson (40), Duncan and Whitby (18), and Hardy, Jordan, Borts, and Hardy (21) give extensive summaries of the literature and deal with many aspects of the problem. The generic name 'Brucella' was suggested by Meyer and Shaw (30), while Huddleson (25) suggested that the three species of the organism be known as *Brucella melitensis*, *Brucella abortus*, and *Brucella suis*.

Various attempts have been made to produce satisfactory tests for the differentiation of the various species in the group. Serological methods have been used by Evans (20), while Huddleson (24) showed that the majority of strains of *Br. abortus* isolated from bovines required an increase in carbon-dioxide tension before satisfactory growth conditions were established. Again Huddleson (25) suggested the use of various concentrations of the bacteriostatic dyes, and he found that thionin added to the culture medium, liver-infusion agar, in a concentration of 1/25,000 inhibited *abortus*, but not *suis* variety, while methyl violet in a 1/100,000 dilution and basic fuchsin in 1/25,000 inhibited *Br. suis*, but not *Br. abortus*.

¹ Received December 5, 1931.

Again Smith (36) and Cotton (12) have found that *Br. abortus* (porcine) is more virulent for guinea-pigs than the bovine variety; while McAlpine and Slanetz (28) maintain that all *Brucella* strains, except the bovine strain of *Br. abortus*, are able to utilize glucose in culture medium. Various investigations on the above methods show that there is no unanimity, and that so far no single test or group of tests is available for the determination of the particular type.

In this country a number of clinical cases have been reported by Byam (10), Bamforth (3), Wordley (42), Manson-Bahr and Willoughby (27), Thompson (37), Charles and Warren (11), Bloxsome and Davey (6), Harrison and Wilson (22), Davis and Anderson (17), Macarthur and Wigmore (29), Williams and Sladden (39), Wishart and Gibson (41), Baxter (5), Scott (31), Cruickshank and Cruickshank (13), Broadbent (7), and Shera (33).

Again Harrison and Wilson (22) in Manchester examined 998 sera submitted for the Wassermann reaction, and found that 50 (5 per cent.) agglutinated *Br. abortus* in dilutions varying from 1/10 to 1/80; whereas Cruickshank and Barbour (14) examined 1,522 sera from patients in the Royal Infirmary, Glasgow, and found that 36 specimens agglutinated *Br. abortus* in a dilution of 1/20 or more.

Scope of Work

In order to obtain some idea of the prevalence of infection of *Br. abortus* in the north-east of Scotland, all specimens of sera submitted for the Widal reaction by medical practitioners and from cases within the various hospitals were tested for agglutinins for *Br. abortus* and *Br. melitensis* as well as for agglutinins for the 'H' and 'O' antigens of the typhoid-paratyphoid organisms. It was apparent that cases of undulant fever must be occurring from time to time, but that the indefinite symptoms associated with the disease made it extremely difficult to recognize without assistance from the Laboratory. Further, by testing a series of sera submitted for the Wassermann reaction, some idea of past infections could be obtained. The results of these various tests have shown that undulant fever exists as a definite disease entity in this community.

Methods

In so far as the investigation of all suspicious human cases was concerned, the following tests were carried out. In the first instance the sera were tested for agglutinins for suspensions of *Br. abortus* and *Br. melitensis*. The agglutination tests were carried out by the macroscopic method in Dreyer tubes, dilutions of the patient's serum ranging from 1/12½ to 1/3,200 being employed. Then a volume of the organismal suspension (as supplied by the Standards Laboratory, Oxford) was added, the final dilutions ranged from 1/25 to 1/6,400, and all tests were incubated at 52° C. for four hours before

a final reading was made. When possible, with cases in hospital or in the neighbourhood of the city and with the co-operation of the medical man in attendance, patients were visited and the blood obtained was directly inoculated in 5 c.c. quantities into two flasks containing 100 c.c. of Huddleson's liver broth and into two bottles each containing 0.05 c.c. of 20 per cent. sodium citrate solution. Specimens of urine were centrifugalized and the deposits were spread over plates of liver agar. The faeces were latterly treated by the method suggested by Amoss and Poston (2), and liver-agar plates were then incubated. All specimens were set up in duplicate, one series being incubated in vessels to which 10 per cent. carbon dioxide had been added and the other series was incubated in the normal atmosphere.

The apparatus used to enable the percentage of CO_2 to be rapidly adjusted is illustrated in Plate 20. It consists of a large vacuum jar A, 12 in. in height by 6 in. in diameter. When the cultures have been placed inside, the jar is connected by a T-tube to a mercury manometer B with an open end, and then to a mercury valve C. With taps T1 and T2 open, the air is exhausted by means of a vacuum pump through T3. When a certain percentage of air has been removed, air bubbles pass back through the glass tube D, the end of which is immersed in the mercury in vessel C. The end of this tube (D) is immersed in the mercury to a depth which is just sufficient to maintain a negative pressure of 8 cm. of mercury in the manometer. Tap T2 is then closed and the valve C detached. Tap T2 is then connected to a Kipps's apparatus generating CO_2 , and sufficient gas is passed into jar A to re-establish normal atmospheric pressure. The extraction of air to give a negative pressure of 8 cm. of mercury allows the admission of just slightly more than 10 per cent. carbon dioxide, and variations in volume due to water vapour and changes in the barometric pressure may, for all practical purposes, be discounted.

The plates and culture tubes were incubated for a period of three days at 37°C . before being examined. Subcultures were then made or, if necessary, the blood cultures were incubated for another period of three days before making a further examination. Plate cultures from the urine and faeces were incubated for six days before being finally discarded, but blood cultures were kept for periods ranging from two to three weeks. From cases residing at a considerable distance from the Laboratory the medical practitioners sent blood for culture purposes in Behring venules containing sodium citrate, this citrated blood being transferred to liver broth on arrival at the Laboratory.

In addition to cultural tests, two guinea-pigs were inoculated intraperitoneally with citrated blood and urine. The animals were killed, one after a period of one month and the other after a period of two months. Their blood sera were tested for agglutinins for *Br. abortus*, and cultures were made in duplicate on liver-agar plates from the spleen and liver, one set again being incubated in the 10 per cent. carbon-dioxide atmosphere and the other in the normal atmosphere.

Further, in an effort to trace the source of infection, inquiry was made regarding the association of the patients with goats, cows, and pigs infected with *Br. abortus*, and the possible ingestion of infected milk and milk products. Samples of milk were accordingly obtained, whey agglutination tests were carried out, and here again two guinea-pigs were inoculated subcutaneously with the deposit from 100 c.c. of milk sample, and thereafter the animals were treated in the same method as described for human cases.

Clinical Cases of Undulant Fever

For the purpose of this investigation, all blood specimens submitted for the Widal reaction were also tested for agglutinins for *Br. abortus* and *Br. melitensis*. Accordingly, since 4.12.28, 373 specimens sent in from cases with various types of 'fever' have been so tested. In all, eleven specimens were found to contain agglutinins for *Br. abortus* in a dilution of 1/100 or more. On investigation, however, one case with an agglutinin titre of only 1/100 was not definitely suggestive of infection due to *Br. abortus* and was excluded from this series. Thus only ten or 2.72 per cent. of cases have been found to have a fever actually due to infection with *Br. abortus*. A brief description of the clinical history and bacteriological findings will now be given.

Case 1. Miss M. McA., aged 24½ years. On 5.7.29, patient came home from work with signs of fever—headache and shivering—and took to bed. Backache began a day or two later, and the pain and shivering feelings continued for about two weeks and were a most prominent feature of the case. The fever was apparently of a continued type for three or four days and then remittent for the next fortnight. During the first week of the illness, the stools were loose with no excessive mucus, but they were very foul-smelling; thereafter constipation was the rule. Sweating was excessive during the first three weeks of the illness, while pains referable to the abdomen and bones were present. She slept well during the first week after the onset, but later became very sleepless. Throughout the whole course there were no symptoms referable to heart or lungs. Altogether she was confined to bed for six weeks and was off work for three months.

Case 2. C. G., a farmer aged 42 years, had several small pimples on the back of his neck on 7.1.30, and in a few days he had difficulty in moving his neck because of stiffness; this was followed in a day or two by general malaise with considerable pains in his limbs. From 12.1.30 to 19.1.30 the patient was partially confined to bed. Eventually on 20.1.30 he was totally confined to bed and complained of headache, pains in left hypochondriac region, constipation, and fever. At this time there was a definitely glandular enlargement in the right cervical region, and the temperature was 101° F. Later the spleen became slightly enlarged and the patient developed a slight urticarial rash. From January 20th to 30th the temperature at noon varied from 101°–103° F., and from this point until it became normal on 16.2.30 its variations are shown in the Chart. Altogether the illness lasted for a period of five weeks.

Case 3. Wm. M., aged 32, a master baker, commenced to feel ill about 15.1.30, but continued to work until 15.2.30 when he became confined to bed. He continued to run a remittent temperature ranging from 101°-103° F. for some days, then a remission occurred, followed by a further attack of fever which subsided and then recurred. This attack was followed by another remission and another recurrence of fever. During the periods of pyrexia the patient complained chiefly of headache, pains in the back and limbs, and excessive sweating. The chest and abdomen showed no abnormal features at any period. Altogether this man had an illness lasting about three and a half months.

Case 4. Mrs. R., aged 25 years. The illness commenced on 9.5.30 with fever, generalized pains in body, and severe headache, and these continued two weeks, when a remission of the illness occurred. This remission lasted about one week and the patient felt so much better that she was allowed up for a short period, but a relapse occurred and an intermittent fever continued for another period of three weeks, when the patient commenced to convalesce. Throughout the course of the illness the patient had no symptoms referable to an affection of any particular organ. The spleen appeared to be definitely enlarged, and at one period there was a slight diarrhoea. After an illness of six weeks convalescence was uneventful.

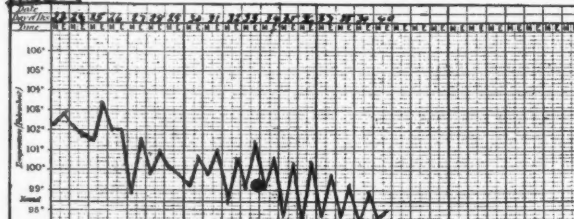
Case 5. W. S. H., aged 32. The illness commenced on 29.7.30 with feverishness, headache, and pain behind the eyeballs. These symptoms continued, and in addition the patient commenced to sweat profusely and to have a very poor appetite. The spleen became definitely enlarged, palpation of the abdomen showed generalized tenderness, and there was marked constipation. Otherwise physical examination failed to reveal signs of organic disease. The temperature usually reached 103° F. every evening, but the pulse remained comparatively slow at 80. Eventually on 12.8.30, after a febrile attack lasting two weeks, the temperature returned to normal and convalescence was uneventful.

Case 6. M. S., a female aged 22, was a nurse in a county fever hospital. Her illness commenced on 4.11.30 with symptoms of general malaise, headache, and fever. These symptoms continued and in addition there occurred chest pains and abdominal discomfort. Physical examination failed to show any definite evidence of intrapulmonary disease, and apart from constipation there were no definite abdominal signs of any importance, spleen and liver being normal in size. Towards the end of the third week a macular eruption developed in the upper chest and neck. The temperature eventually became normal on 26.11.30, and thereafter convalescence was uneventful. The variations in temperature are shown on the accompanying temperature chart.

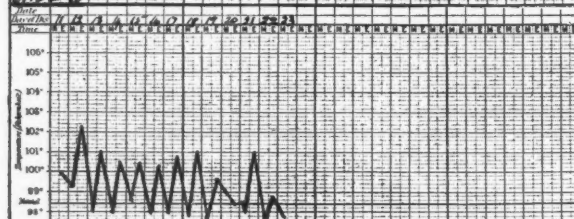
Case 7. A. R., a male aged 17 years, was taken ill on 8.3.31 with symptoms of fever accompanied at first by headache, generalized pains, and profuse sweating. He ran an intermittent temperature for over four weeks, and was eventually admitted to a cottage hospital for observation. During the whole period of his illness, with the exception of headache for the first few days, he complained of nothing. His temperature occasionally reached 103° F., but his pulse-rate remained relatively slow. Repeated careful physical examination failed to show anything abnormal, and his general condition remained good. Eventually his temperature reached normal limits on 4.5.31, two months after the onset of the fever.

Case 8. Male aged 14 years and brother of Case 7. This boy's illness commenced on 28.4.31, fifty-one days after the onset of the brother's illness, with the usual symptoms, fever, headache, and sweating. Despite the fact that the brother was ill, the medical attendant was not sent for immediately,

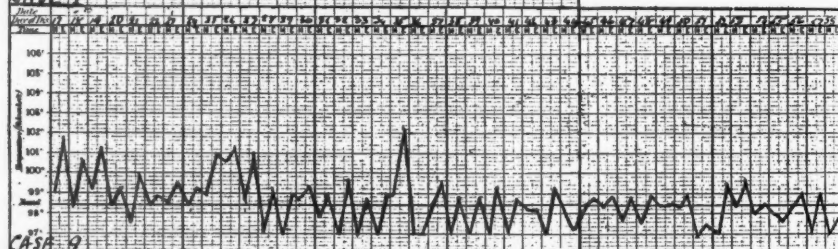
CASE 2



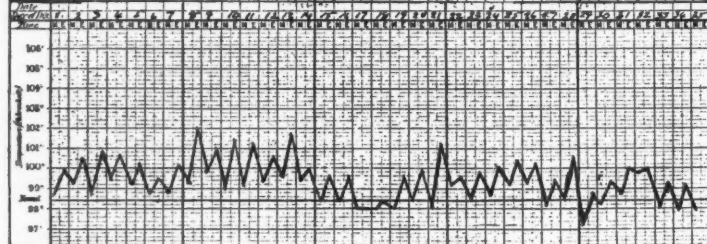
CASE 6



CASE 7



CASE 9



Temperature Charts.

and the patient returned to work on 6.5.31 and continued to work until a relapse occurred on 20.5.31. He was then seen by his doctor on 21.5.31 who found the temperature to be 103° F., and his symptoms were confined to headache and slight generalized pains. Physical examination showed no abnormalities in the chest or in the abdomen apart from slight tenderness over the gall bladder. The patient was admitted to the cottage hospital,

but two days after admission the temperature became normal and convalescence was uneventful.

Case 9. Mrs. S., aged 30 years, was taken ill on 14.9.31 with symptoms of fever, headache, and profuse sweating. Physical examination failed to show any evidence of organic disease in chest or abdomen, and at no time during the course of the illness could localizing symptoms be elicited. The temperature continued to vary between 102° F. and 98.6° F., and the complete chart shows very definitely the undulating character of the fever (Chart of Case 9). After an illness of five weeks the fever subsided and convalescence was uneventful.

Case 10. Mrs. T., aged 39 years, was taken ill on 14.10.31 with fever and general malaise. There was no definite pain, no abdominal symptoms except lack of desire for food. The intermittent fever continued, and on 1.11.31 the medical attendant sent a specimen of blood for the Widal reaction. The serum failed to agglutinate any organisms of the typhoid-paratyphoid group but agglutinated *Br. abortus* to 1/200. The patient was then admitted to hospital, where it was found that the temperature was 101.5° F. and the pulse-rate 106. Apart from the fever, physical examination failed to show any abnormalities with the exception of a profuse macular skin eruption, and this eruption was present on the mucous membranes of the mouth and throat as well. Two days later the fever subsided, the rash gradually disappeared, and thereafter convalescence was uneventful.

The clinical aspects of these ten cases reported show how difficult it would be to arrive at a diagnosis on the basis of a physical examination and on the correlation of symptoms. It would appear that a possible diagnosis might be arrived at from a study of the temperature chart in the undulating type of the disease, but the diagnosis in many cases could only be suggested by the exclusion of such diseases as typhoid fever, broncho-pneumonia, acute rheumatism, tuberculosis, infective arthritis, Hodgkin's disease, and malignant disease. The fever in most of the cases in this series commenced with remittent characteristics and ended in an intermittent fashion. In Cases 3 and 9 the fever was definitely undulating in character, and four temperature charts of Cases 2, 6, 7, and 9 are given to illustrate the various features. In all cases headache was complained of markedly, especially at the commencement of the illness, while general aching was also frequently present. Sweating was also a prominent symptom and occurred during the afternoon or night, the patient awakening to find himself (or herself) bathed in perspiration. Chest symptoms were entirely absent, but abdominal signs consisting of varying degrees of anorexia, constipation, and vague abdominal discomforts and tendernesses were seen. After the prolonged febrile period, convalescence was uneventful and normal health was rapidly established.

Serological and Bacteriological Findings

The serological findings are summarized in Table I, from which it will be seen that in the first instance the diagnosis was based on the agglutination test. In five cases it was possible to obtain repeated specimens of serum

during the course of the illness, and a very definite increase in the amount of agglutinins present was obtained; thus in Case 2 the titre for *Br. abortus* rose from less than 1/25 to 1/1,600, in Cases 4, 5, and 6 there was an increase of 100 per cent. in the amount of agglutinins present in the first as compared with the second specimens, while in Case 10 an increase of 400 per cent. was recorded. These results are significant since the specimens were all tested against Oxford standard suspension with the same agglutinable factor. Further, in Cases 7 and 8 the second blood specimens were obtained after normal health was established, and here the specimens showed a marked decrease in the titre. The specimens of sera have consistently agglutinated *Br. melitensis* (Oxford standard suspension) to a less titre than *Br. abortus*, there being usually 100 per cent. difference in the end titre; this, however, only means a difference of one dilution by the method used. Further, absorption tests showed that by absorbing the various sera with a heavy suspension of *Br. abortus* all the agglutinins for *Br. abortus* could be readily removed.

The cultural examination of the various specimens has not been so successful, but this can probably be accounted for by the fact that the illness in most cases was well advanced before a diagnosis was made on serological grounds, that all but two cases were away from hospital, and only a further two cases actually occurred in the city. The delay in the cultural examination of the various specimens definitely prejudices a possible successful result. However, in three cases it was possible to obtain the infecting organism. Thus in Case 5 guinea-pig inoculation showed the organism present in the urine; while in Cases 6 and 10, both of which were admitted to hospital, *Br. abortus* was obtained from the faeces in Case 6 and from the blood in Case 10. All strains of *Br. abortus* thus obtained showed the normal characteristics of this organism. Primary cultures were only obtained by culturing in an atmosphere containing 10 per cent. carbon dioxide, and the organisms so obtained agglutinated to the full titre of a serum prepared for *Br. abortus*, and in addition completely absorbed the agglutinins from this serum.

Source of Infection

In the first case, a native of the city, the possible sources of infection were not determined. In the second the clinical history suggested that the infection had occurred through an abrasion in the skin in the cervical region. This Banffshire farmer had an outbreak of abortion among his cows and had been constantly in attendance on infected animals. Case 3 occurred in Ross-shire, the patient being a master baker; a sample of the milk supply could not be obtained and inquiry failed to show any recent case of epidemic abortion in the dairy herd from which the milk supply was obtained.

Case 4 was a farm servant's wife living in Kincardineshire. In this

instance the regular milk supply was examined, but the whey agglutination test failed to show agglutinins for *Br. abortus* and guinea-pigs also failed to show *Br. abortus*. Inquiry showed, however, that this patient had partaken of milk from several sources other than the regular supply.

Case 5 was a city postal servant who had been on holiday some three weeks, visiting various parts of the country, and who was taken ill just after returning to Aberdeen.

Case 6 was a nurse in a county fever hospital. The milk supply was examined, samples being obtained from each of the fourteen cows comprising the herd. The whey agglutination tests were positive in two instances. One whey sample agglutinated *Br. abortus* to a dilution of 1/400 and the other to a dilution of 1/800. Guinea-pigs inoculated later showed *Br. abortus* to be present in both these specimens.

Cases 7 and 8 were brothers residing in Banffshire. Here the milk sample was obtained from two sources. The whey agglutination test was carried out with the mixed milk from each farm. One specimen agglutinated *Br. abortus* to a dilution of 1/200 and the other failed to show any agglutinins. *Br. abortus* was later recovered from the animals inoculated with the milk which contained the agglutinins.

Case 9 was a married woman, residing in Aberdeenshire, who obtained the milk supplies for the household from three sources. The mixed milk sample from each of these dairy farms was obtained, and the whey agglutination tests showed that two specimens contained agglutinins for *Br. abortus*, one specimen agglutinating to a dilution of 1/200 and the other to a dilution of 1/800. Guinea-pig inoculation showed that both samples contained *Br. abortus*.

Case 10, a married woman also living in Aberdeenshire, changed her milk supply on 1.10.31 and her illness commenced on 14.10.31. Samples of milk were obtained from the source previous to 1.10.31 and from the new source. The first supply was obtained from a herd containing only three cows, while the second supply was obtained from a herd containing eighteen cows. The whey agglutination tests with the mixed milk from the first source gave a negative result. Seven samples were obtained from the eighteen cows in the second herd. Here it was found that a cow had actually recently aborted, and the whey agglutination test was positive in a 1/100 dilution; while the test carried out on the milk from a group sample from five cows gave agglutination in a dilution of 1/400. The animal inoculation tests have not yet been completed, but if they prove positive then the incubation period of the disease in this case, provided the infection was derived from the milk, is limited to a period of fourteen days.

The milk supply, therefore, seems to be the most likely source of infection in these cases. Practically the only other milk product used for food purposes was cheese; no goats were associated with any of the cases, and the possibility of infection from pigs also seems to be unlikely.

Agglutinins for Br. abortus and Br. melitensis in Sera submitted for the Wassermann Reaction

In order to obtain evidence of the incidence of infection, the sera from 1,446 individuals submitted for the Wassermann reaction were tested for their agglutinins for *Br. abortus* and for *Br. melitensis*. The sera were tested in final dilutions varying from 1/25 to 1/1,600, and the results are summarized in Table II, from which it will be seen that only sixty-six sera showed agglutinins for *Br. abortus* and only thirty sera for *Br. melitensis* in a dilution of 1/25 or more. Furthermore thirty-six specimens agglutinated *Br. abortus* at 1/25, twenty-two at 1/50, five at 1/100, two at 1/200, and one at 1/400; while twenty-three specimens agglutinated *Br. melitensis* at 1/25, four at 1/50, two at 1/100, and only one at 1/200 dilution of the sera. Thus if agglutination at a dilution of 1/100 or more is regarded as of some significance, then only eight sera showed such titres for *Br. abortus* and three for *Br. melitensis*. In Table III the titres of the sera for *Br. abortus* are compared with those for *Br. melitensis*, and in many cases it was found that the titre of *Br. melitensis* was 100 per cent. or one dilution less than for *Br. abortus*; in some instances, however, the end titres for both suspensions were the same. The tests were carried out with Oxford standard suspensions, and the factors for converting the end titre into agglutinin units were 1.9 and later 2.3 for suspensions of *Br. abortus* and 2.5 for all suspensions of *Br. melitensis*.

It was possible to obtain the age and sex of about half the patients from whom the samples were taken, and the agglutination results were therefore correlated with age group and sex, the results being given in Table IV. Thus twenty-five sera from 371 males and twelve sera from 348 females agglutinated *Br. abortus* in a dilution of 1/25 or more, making a total of thirty-seven out of a total 719 specimens showing some amount of agglutinins; whereas in the complete totals sixty-six samples out of 1,446 contained demonstrable agglutinins. Again, in the male age-group, the highest percentage of positive reactions was found in the sera from the group 21-30 years, whereas in the female group it was in the group 41-50 years. When the groups were combined the majority of the sera containing agglutinins were found to occur in the age-group 11-50 with the maximum percentage in the group 41-50.

Again, if agglutination in a dilution of 1/100 or more is regarded as possibly indicating some previous infection, then only eight sera out of the total of 1,446, or 0.57 per cent., showed the requisite amount of agglutinins. Accordingly, a particular inquiry was made into the individuals from whom these blood specimens were obtained, and the results are given in Table V. Here it was found that all samples were obtained from males between the ages of 23 and 55 years. Five of the specimens agglutinated *Br. abortus* to a dilution of 1/100, two samples to 1/200, and one sample to 1/400.

The occupations of the three individuals whose sera agglutinated *Br. abortus* in a dilution of 1/200 or more were found to be farm servants in two instances and a butcher in the third. Further inquiry showed that the individual whose blood agglutinated *Br. abortus* to a dilution of 1/400 had had a febrile disease lasting about two months about six months prior to taking the blood specimen, and that the condition was regarded as being due to tuberculosis, but later no evidence of active tuberculous disease could be found.

Discussion

The cases of undulant fever illustrate the difficulties of diagnosis from the clinical point of view. The complete lack of a definite symptom complex emphasizes the need of laboratory investigation, and further, apart from obtaining a positive agglutination reaction the isolation of the actual organism requires a complete and repeated bacteriological examination of blood and excreta.

In the cases encountered so far the sexes have been represented equally, the ages of the females varying from 22-39 years and the males from 14-42 years. This age incidence corresponds closely with what has been found in the United States and Denmark. The remarkable immunity of children, especially since they are the main consumers of milk, has been emphasized by American and Continental workers.

As regards the agglutination test the instructions issued with the *Br. abortus* standard agglutinable suspensions from Oxford state that a standard of ten units may be taken as establishing a high probability of present or past infection, and this corresponds with standard agglutination in a dilution of 1/25 of the patient's serum. According to this, 4.16 per cent. of individuals from whom the Wassermann sera were obtained showed evidence of past infection. This, however, seems to be an over-estimate of the number of cases, and for the present it does not seem to be warranted to suggest a diagnosis of undulant fever when agglutination is obtained with this dilution of the serum. When, however, a titre of 1/100 or more is obtained, then it should be necessary to follow up the case and apply further serological and bacteriological tests where the clinical findings point to the necessity of such a procedure. It must also be borne in mind that, if the blood sample were obtained early in the disease, the agglutination titre might only be 1/25 or 1/50 and yet later might reach quite a high limit.

As regards the actual reading of the agglutination test no great difficulty has been experienced. In many of the agglutination tests, especially when the titres have reached 1/200, 1/400, or higher, the pro-zone phenomenon has been encountered; that is, despite the fact that agglutination was obtained in the higher dilution, no agglutination might be obtained in the 1/25 or 1/50 dilutions. This phenomenon, however, is less marked when the Oxford

standard suspensions are used than when certain living cultures are employed for the tests. The results, however, indicate that it is necessary to titrate the sera to a dilution of 1/1,600 to 1/3,200 to avoid any possibility of misinterpreting results which would be obtained if only the lower dilutions of the sera were employed.

The investigation suggests that the majority of infections must occur through drinking raw milk or eating raw-milk products, since in only one instance (Case 2) do the clinical findings indicate that the organism gained admission through an abrasion on the skin. An investigation has been made into the prevalence of *Br. abortus* in raw-milk supplies. These results will be reported in detail later, but it has been found that 28.6 per cent. of samples of milk as received from the dairy farms contain *Br. abortus*. It would therefore appear that there must be a very high rate of immunity in human beings for this organism, or that the bovine type of *Br. abortus* is relatively avirulent for the human. American workers have calculated that of those exposed to infected milk 1.4 per cent. show evidence of infection but only 0.8 per cent. show evidence of active infection. It has also been shown by American and Continental workers that the porcine type of *Br. abortus* is relatively more virulent for man than the bovine type, but so far it has not been possible to obtain evidence of the prevalence of this type. Various veterinary men have stated that epidemic abortion in swine is not prevalent in this part of the country.

As regards prophylaxis, Hasseltine (23) says that 'It makes no difference whether a patient receives a bovine, porcine, or caprine *Brucella* infection through the raw milk he consumes, the fact that he contracts a preventable disease makes this matter of first importance.' Arnold (1) maintains that milk requires to be pasteurized at 140° F. for forty minutes before *Br. abortus* is killed. Our experience here has shown that pasteurization by the 'flash-point' methods is ineffective in destroying *Br. abortus*, whereas pasteurization by modern 'holding' methods ensures total destruction of this organism. The prophylaxis of this infection could be accomplished, so far as milk-borne infections are concerned, by efficient pasteurization, since elimination of infected animals from dairy herds would almost seem to be an impossible procedure in the present circumstances.

Summary

The clinical, bacteriological, and serological findings in ten cases of undulant fever are described.

Five infections occurred in males whose ages ranged from 14 to 42 years and five in females aged 22 to 39 years.

Possible methods and sources of infection have been examined. It is believed that the disease is mainly conveyed by drinking infected milk.

Of 373 specimens of serum sent for examination from cases of 'fever', eleven specimens agglutinated *Br. abortus* in a dilution of 1/100 or more.

Ten specimens were believed to have been derived from cases infected with *Br. abortus*—0·26 per cent. of cases of all types of fever.

The sera obtained from 1,446 individuals have been examined for agglutinins for *Br. abortus* and *Br. melitensis*; sixty-six specimens agglutinated *Br. abortus* in a dilution of 1/25 or more and thirty agglutinated *Br. melitensis* in a dilution of 1/25 or more. Only eight specimens or 0·5 per cent. agglutinated *Br. abortus* in a dilution of 1/100 or more. The significance of these results has been discussed.

The author is indebted to many medical men for supplying information and specimens, and to the Medical Research Council for a personal grant.

TABLE I
Serological Findings in Cases of Undulant Fever

Case.	Date.	Result of Agglutination Test.			
		<i>Br. abortus.</i>		<i>Br. melitensis.</i>	
		Titre.	Aggn. Units.	Titre.	Aggn. Units.
1	20.7.29	1/3200	1683	1/1600	640
2	22.1.30	< 1/25	0	< 1/25	0
	13.2.30	1/200	86	1/200	80
	16.2.30	1/1600	695	1/800	320
3	15.2.30	1/12800	5564	1/3200	1280
4	27.5.30	1/3200	1391	1/800	320
	2.6.30	1/6400	2782	1/800	320
5	7.8.30	1/200	100	1/100	50
	19.8.30	1/3200	1600	1/1600	800
6	26.11.30	1/800	400	1/800	400
	27.11.30	1/1600	800	1/1600	800
	12.12.30	1/1600	800	1/800	400
7	17.4.31	1/12800	6400	1/12800	6400
	22.5.31	1/800	400	1/400	200
8	22.5.31	1/3200	1600	1/800	400
	8.6.31	1/800	400	1/400	200
9	1.10.31	1/12800	6400	1/6400	3200
10	31.10.31	1/200	100	1/100	50
	2.11.31	1/400	200	1/200	100
	10.11.31	1/800	400	1/400	200

TABLE II
Results of Agglutination Tests on Sera submitted for the Wassermann Reaction

Dilution.	No. of Sera agglutinating.	<i>Br. abortus</i> : % agglutinating.	No. of Sera agglutinating.	<i>Br. melitensis</i> : % agglutinating.
0	1380	95·39	1416	97·92
1/25	36	2·49	23	1·59
1/50	22	1·55	4	0·28
1/100	5	0·36	2	0·14
1/200	2	0·14	1	0·07
1/400	1	0·07	0	0·00
1/800	0	0·00	0	0·00
	1446	100·00	1446	100·00

TABLE III

Comparison of Agglutination Results with Suspensions of Br. abortus and Br. melitensis

Agglutination with <i>Br. abortus</i> .		No. of Sera agglutinating with <i>Br. melitensis</i> .					
No. of Sera.	Dilution.	Dilutions.					
		1/400	1/200	1/100	1/50	1/25	1/25
1380	1/25	0	0	0	0	0	1380
36	1/25	0	0	0	0	10	26
22	1/50	0	0	0	1	11	10
5	1/100	0	0	0	3	2	0
2	1/200	0	0	2	0	0	0
1	1/400	0	1	0	0	0	0
1446							

TABLE IV

Age Distribution of Agglutination Reactions 1/25-1/400

Age Group.	Males :			Females :			Male and Female :		
	No. of + Sera.	Total Sera.	% Positive.	No. of + Sera.	Total Sera.	% Positive.	No. of + Sera.	Total Sera.	% Positive.
1-10	3	67	4.4	0	68	0	3	135	2.5
11-20	2	34	5.8	3	45	6.6	5	79	6.3
21-30	9	99	9.0	6	127	4.7	15	226	6.6
31-40	4	61	6.5	1	57	1.7	5	118	4.2
41-50	4	48	8.3	2	29	6.8	6	77	7.8
51-60	2	29	6.8	0	15	0.0	2	44	4.5
61+	1	33	3.3	0	7	0.0	1	40	2.5
	25	371		12	348		37	719	

TABLE V

Cases showing Agglutinins in Sera in a Dilution of 1/100 or more for Br. abortus

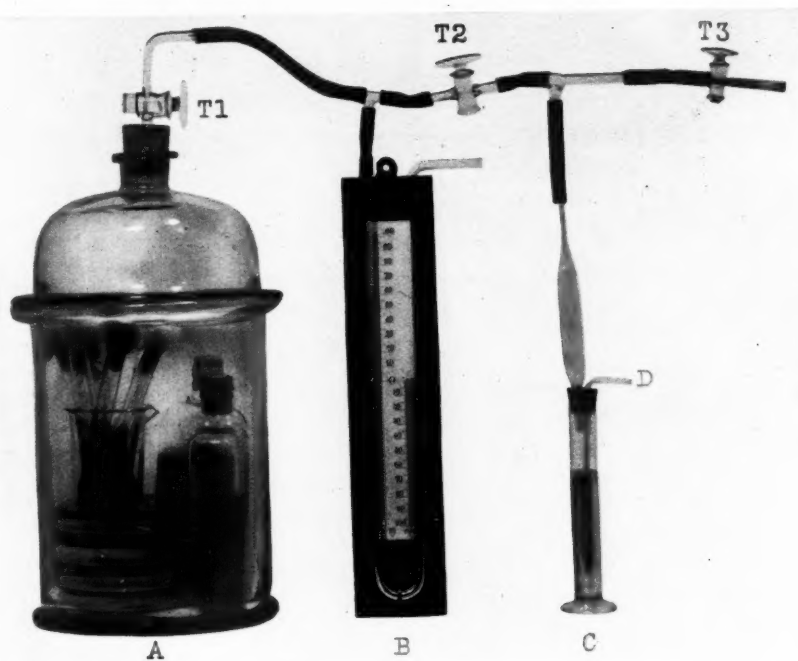
Case.	Address.	Sex.	Age.	Occupation.	Agglutination Titre of Serum.
1	Aberdeen	M	31	News vendor	1/100
2	Aberdeen	M	46	Rag merchant	1/100
3	Aberdeen	M	49	Farm servant	1/200
4	Aberdeen	M	32	Contractor	1/100
5	Banff	M	26	Farm servant	1/100
6	Aberdeen	M	55	Night watchman	1/100
7	Aberdeen	M	23	Butcher	1/200
8	Aberdeenshire	M	30	Farm servant	1/400

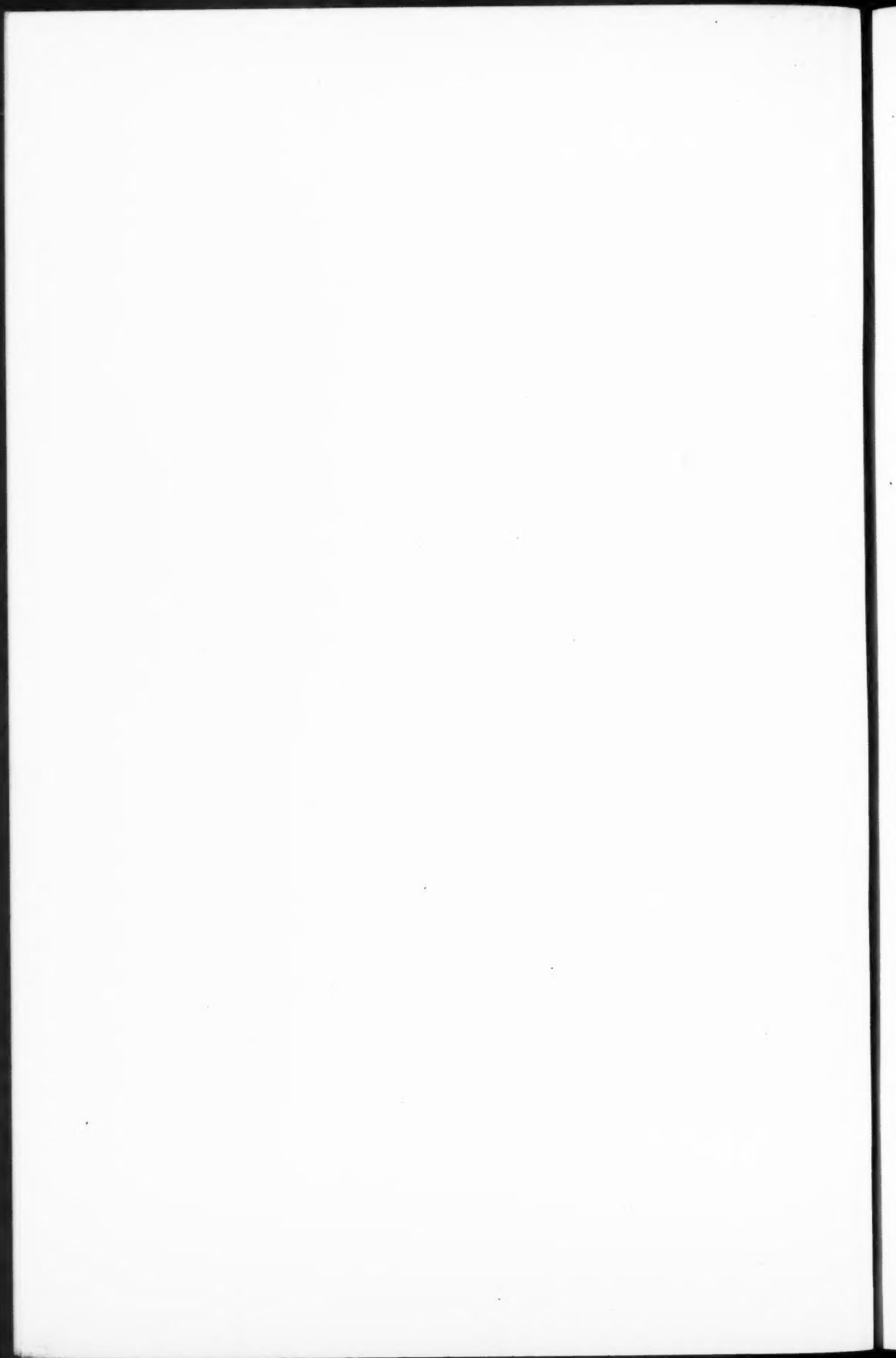
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SOME OBSERVATIONS ON PERSISTENT BRADYPNOEA IN A CASE OF POST-ENCEPHALITIC PARKINSONISM¹

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With Plates 21 to 24

THE case which we are about to describe appeared in the epidemic encephalitis clinic of Professor Arthur Hall, who has kindly furnished us with the following note on bradypnoea in encephalitis:—‘Although the statement will be found in most text-books and monographs on this subject, that post-encephalitic respiratory disorders include bradypnoea, yet on looking farther into the matter it is evident that the case of bradypnoea which originally gave rise to this statement hardly deserves the name. Succeeding writers have largely followed the classification of Marie, Binet, and Levy (1) who published one of the earliest general reviews of the various respiratory anomalies occurring in encephalitis. They divided them into three groups. One of these was:—(a) troubles respiratoires proprement dits; this was described as follows, “Ceux-ci consistent essentiellement en phénomènes de polynée (ou tachypnée) accessoirement seulement en phénomènes d’apnée ou de bradypnée.” Later, under the same heading, there follows this paragraph:—“La bradypnée et l’apnée n’ont été constatées par nous que dans un cas qui est le suivant: la respiration est irrégulière; on se compte 15 à 20 par minute; la compression des globes oculaires la fait descendre à 10 par minute.” From time to time cases of breath-holding accompanied by other muscular phenomena have been described and classed under bradypnoea, but so far as I can ascertain, no case of permanent or continuous slow breathing—(true bradypnoea)—such as the present one, has been as yet recorded in a person suffering from chronic epidemic encephalitis.’

We wish to point out, however, that bradypnoea has been observed in a healthy individual, for Briggs (2) reports some observations made on a footballer with a resting respiratory rate of three per minute; he exhibited a high standard of physical fitness according to tests which were being carried out on a large series of miners and recruits.

The case which we have investigated is that of a male, now aged 32 years, who had his acute attack of encephalitis in March 1924 but did not come

¹ Received January 19, 1932.

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under Professor Hall's care until September 1928. Some of the features of post-encephalitic Parkinsonism, such as slow movements, tremors, and muscular rigidity, were quite pronounced, and it was also observed that the respiratory rate was unusually slow, four or five per minute. Since then the man has been under observation, first as an in- or out-patient at the Sheffield Royal Hospital and later at the South Yorkshire Mental Hospital, to which he was subsequently transferred on account of the development of mental changes.

On clinical examination it was readily seen that the respirations were deeper than normal. The thoracic component of the respiratory movements appeared to be increased more than the abdominal one. Both respiratory phases were prolonged, expiration more than inspiration. On auscultation the respiratory murmur was found to be continuous during inspiration, but towards the end of expiration it was interrupted by short pauses imparting a coarsely saccade quality to the sound. This was best heard over the trachea. There was no cyanosis or emphysema.

Such a case presented interesting features from both pathological and physiological standpoints. Certain problems naturally arose. On the one hand, was there any relationship between the disturbance in the mechanism regulating the respiratory movements and lesions in the nervous system and changes in muscle function known to occur in epidemic encephalitis, and, if so, what was its nature; and, on the other hand, how was the pulmonary ventilation adequately maintained, and how did the response of the respiratory mechanism under physiological and experimental conditions compare with that obtained in an individual who breathes at a normal rate? The investigations recorded in this paper are concerned more particularly with the aspects of disturbed function and adaptation to physiological requirements.

Observations

Graphic records of the respiratory movements were obtained by adjusting to the thorax a Marey's pneumograph communicating with a tambour which moved a writing point in contact with smoked paper on a kymograph. With this type of pneumograph the amplitude of the excursions of the writing lever corresponding to the respiratory movements varies according to the manner in which the instrument is applied to the chest. Uniformity in this respect could not always be ensured. Therefore, in so far as they record the range of the respiratory movements, the records may not be strictly comparable one with another, though in any one record individual respiratory excursions do bear comparison. All the records are to be read from left to right; downstroke represents inspiration, upstroke expiration, time marker nine seconds intervals.

Rate of respirations. Plate 21, Fig. 1, consists of two records of the respiratory movements on separate occasions with the subject at rest seated in a

chair; for comparison with these one record from a normal individual is included. The difference is striking. The average respiratory rate in the normal subject is 10 per minute, Plate 21, Fig. 1c; in the case of bradypnoea it is 4.1 and 3.4 in 1A and 1B respectively. The rate is not uniform. The average rate is 3.8 in the first part of Plate 21, Fig. 1A, and 5.1 in the second part.

The amplitude of the respiratory movements is much greater than normal, but not uniformly so. Another feature in the record is the marked prolongation of expiration. The steep downstroke of inspiration contrasts strikingly with the curved upstroke of expiration; the duration of the former is three to four seconds, that of the latter three or four times as long.

The tidal air was determined by collecting the expired air in a Douglas bag and dividing the volume by the number of respirations during the period of observation, corrections being made for temperature, barometric pressure, and aqueous vapour tension. It was found to vary at different times from 1,200 c.c. to 2,000 c.c. (normal 500 c.c.) But this procedure did not give precise information regarding the variations in the volume of air with individual respirations. In order to observe this, the subject inspired atmospheric air from a large spirometer provided with an appropriate scale. The rate of breathing was so slow that adequate time was available for taking the readings after each inspiration. The period of observation lasted sixteen minutes, and the average respiratory rate during this time was three per minute. The figures set out in Table I express the volume of air inspired in each of twenty successive respirations. The largest volume is 2,020 c.c. and the smallest 1,390 c.c., thus showing a variation of 680 c.c., a figure larger than the tidal air in the normal subject.

TABLE I

Volume of Air Inspired during each of Fifteen Consecutive Inspirations

	c.c.	
	1810	
	2020	
	1720	
	1480	
	1980	
	1610	
	1600	
	1860	
	1880	
	1390	
	1870	
	1590	
	1680	
	1870	
	1680	
<i>Average volume</i>	.	1736 c.c.
<i>Maximal volume</i>	.	2020 c.c.
<i>Minimal volume</i>	.	1390 c.c.
<i>Average respiratory rate</i>	.	3 per minute.

In a normal subject with a tidal air of 500 c.c. and breathing at a rate of fourteen times per minute, the minute volume of the expired air is 7 litres. As seen in Table I, the minute volume of the case of bradypnoea is about 5.2 litres. It appears, therefore, that the bradypnoea is only partly compensated by the increase in the tidal air, the minute volume remaining less than normal. Under such conditions, if the pulmonary ventilation is to be maintained adequately, the degree of respiratory exchange between the oxygen and carbon dioxide in the alveolar air and the blood in the lungs must be greater than in the normal subject. The duration of one respiratory cycle is approximately four or five seconds, according to the rate of the breathing, in a normal subject, but when the rate is only three per minute the length of a cycle approaches twenty seconds. During this time oxygen is being taken out and carbon dioxide added to the alveolar air. It is to be expected, therefore, that the concentration of these gases in the alveolar air departs considerably from the normal; the concentration of the carbon dioxide should be greater, that of the oxygen less than normal. A sample of alveolar air collected at the end of an expiration contained 7.93 per cent. of carbon dioxide and 11.3 per cent. of oxygen, as compared with 5.5 per cent. and 14.5 per cent. respectively in the normal.

TABLE II

	Bradypnoea.	Normal.
Respiratory rate	4.4	16
Tidal air	1560 c.c.	450 c.c.
Minute volume	4.5 to 5.5 litres	7.2 litres
<i>Expired air:</i>		
Carbon dioxide	4.93 %	3.3 %
Oxygen	14.35 %	17.2 %
<i>Alveolar air, carbon dioxide:</i>		
After normal inspiration	6.19 %	5.2 %
After normal expiration	7.93 %	5.8 %
<i>Alveolar air, oxygen:</i>		
After normal inspiration	13.10 %	15.5 %
After normal expiration	11.37 %	14.6 %
<i>Plasma bicarbonate: venous blood</i>	70.5 volumes per cent.	
<i>Haemoglobin</i>	95 per cent.	
<i>Red blood-cells</i>	5.5 millions per c.mm.	

To appreciate the significance of these results it is necessary to consider certain aspects of pulmonary ventilation. Normally about 500 c.c. of air are taken into the lungs during each inspiration. Since the volume of the anatomical dead space is calculated to be about 150 c.c., only 350 c.c. of the air inspired will be concerned with the dilution of the alveolar air. As the volume of air in the lungs is approximately 3,000 c.c. it follows that the ingress of 350 c.c. of the atmospheric air will not dilute to any great extent, and therefore the changes in the composition of the alveolar air will vary within narrow limits only. Such changes as do occur will take place every four or five seconds, according to the rate of breathing. But with a tidal

air of 1,500–2,000 c.c. as in this case, a greater proportion of the atmospheric air reaches the alveoli notwithstanding the increase of the physiological dead space which accompanies deep breathing in the normal subject. The alveolar air, therefore, is diluted to a greater extent than occurs with respirations of normal depth. In addition, since the duration of each respiratory cycle is about twenty seconds, and during this time the exchange of carbon dioxide and oxygen between the blood and alveolar air continues, the range of variation in concentration of these gases in the alveolar air during each respiratory cycle must be of a greater order than that observed normally. It has been pointed out previously that the minute volume is less than normal. Accordingly, if the output of carbon dioxide and the consumption of oxygen are normal, the concentration of the former in the expired air should be greater, that of the latter less, than the values normally obtained for these gases. This departure from the normal could only be brought about by changes of a similar nature in the average composition of the alveolar air, i.e. increased carbon dioxide and decreased oxygen percentage. The figures in Table II show that these changes have taken place.

Such an increase in the concentration of carbon dioxide in the alveolar air will raise the tension of this gas and increase the amount present in simple solution in the blood-plasma. Since the hydrogen-ion concentration of the blood depends on the ratio $\frac{H.HCO_3}{B.HCO_3}$, an increase in the carbon dioxide in simple solution must be accompanied with an increase in the carbon dioxide bound as the bicarbonate, if this ratio and the pH of the blood are to remain normal. The alkali reserve or the plasma bicarbonate should be increased. As seen in Table II, this value for the venous blood of the case of bradypnoea is 70.5 volumes per cent., the mean normal figure being 60 volumes per cent.

The physiological response to a sustained diminution in the tension of oxygen in the alveolar air, as occurs in those who live at high altitudes, is an increase in the haemoglobin and the number of red blood-cells. In our case the haemoglobin is 95 per cent. and the red blood-cells 5.5 millions per c.mm.—figures somewhat above the average found in hospital patients not suffering from any blood disease.

Some investigations have been made regarding the behaviour of the respiratory mechanism under certain conditions, physiological and otherwise. These may be considered separately.

Volitional hyperpnoea. As seen in Plate 22, Fig. 2, the subject could breathe more rapidly when asked to do so. The resting rate of 3.4 per minute was increased to 19 per minute; this was followed by a retardation of the original rate to 2.3 per minute, which can be attributed to the hyper-ventilation effected by the increased rate of breathing. Another point of interest relates to the expiratory phases. The duration of expiration is decreased during the period of rapid breathing. It appears, therefore, that not only is volitional control of the respiratory centre intact, but also

that, during the volitional increase in the rate of breathing, the factor which is responsible for the prolongation of expiration when the respirations are slow is no longer predominant when the rate is increased intentionally. Similarly, reflex excitation of expiration, as in coughing, produces a rapid expiratory effort. In Plate 21, Fig. 1B, a tracing of the respiratory movements interrupted by a cough is reproduced.

Speech. It may not be appreciated generally to what degree the nature of the respiratory movements is altered during speech in a normal individual; rate, depth, and rhythm become partially subordinated to the performance of this function. Inspiration becomes deeper, expiration prolonged, the rate and rhythm of both respiratory phases more variable. The extent to which these are influenced depends upon such factors as expression, punctuation, and energy expended. It is not proposed, however, to discuss here the physiological aspects of this relationship. But, as we have been interested in this subject, records of the respiratory movements during speech were obtained from this case, and one of these is reproduced in Plate 22, Fig. 3A, along with one from a normal subject.

In the tracing from the normal individual reading aloud, the totally irregular nature of the respiratory movements is apparent. Inspiration is frequently deeper than normal and is rapidly performed. Expiration is sometimes prolonged and, as shown by the irregular contour of the upstroke, may not be continuous, the interruptions being associated with pauses for emphasis or punctuation and not always followed by another inspiration. It is also manifest that on occasions the degree of pulmonary deflation at the termination of an expiration is greater than normal, the writing point having risen above the base line. The record also shows the respiratory movements when the subject repeated a well-known passage and sang the National Anthem (he was not a trained vocalist).

When the bradypnoeic performed similar exercises interesting features were seen in the records. On reading aloud the respiratory rate was increased to an average rate of 20 per minute. The subject was not reading continuously during the time that the record was transcribed. Oculo-gyric crises, characterized by closure of the eyelids and the turning up of the eyes, occurred at intervals, and during these reading was impossible. Three such crises are indicated on the record, and it is seen that they coincide with the slowing of the respirations. Variations in the amplitude of respiratory excursions are present, and it is shown that the degree of pulmonary deflation or inflation is not uniform when successive inspiratory or expiratory acts are initiated.

When he was requested to repeat the same passage (the Lord's Prayer) and to sing the National Anthem, the subject performed each exercise during single expiratory phases. As seen in the record there was a preliminary inspiration deeper than normal followed by a prolonged expiration which was maintained, notwithstanding the development of an unusual degree of pulmonary deflation. After the end of the singing four seconds

elapsed before the next inspiration occurred. This has been repeated frequently and the records obtained have been substantially the same. In the normal individual three or four respirations are recorded for similar exercises performed at approximately the same rate.

It is not clear why the respiratory rate should increase so much when the subject was reading aloud. The amount of work performed was not sufficient to explain it. We are inclined to attribute it to the influence of higher centres which become effective during the performance of speech. The respiratory centre responds to this higher central control as it does in volitional stimulation.

Sleep. Some observations were made with the subject in bed awake, during natural sleep, and after the administration of omnopon. The records are shown in Plate 23, Fig. 4. It was difficult to maintain a constant adjustment of the pneumograph owing to the involuntary movements during sleep. Re-adjustment could not always be carried out for fear of awakening the subject. The average respiratory rate appears to increase slightly during natural sleep, 4.5 and 5 per minute as compared with 3.7 when lying awake in bed. One hour and a half after omnopon the subject was sleeping deeply and the average rate was 3 per minute. It is apparent that there is a tendency to periodic variations in both the rate and depth of the respirations after omnopon, probably due to a certain degree of anoxaemia resulting from the lower respiratory rate.

Work. An investigation of the influence of work upon the respiratory exchange showed further points of interest. The subject seated on a bicycle-ergometer breathed into a Douglas bag over a known period of time during which the respiratory movements were recorded. Subsequently the observations were repeated while he performed a definite amount of work pedalling against a known resistance. From analyses of the air collected and other data the respiratory exchange for maintenance and the performance of work could be determined. Records of the respiratory movements are shown in Plate 24, Fig. 5. Figures for the experimental observations are set out in Table III.

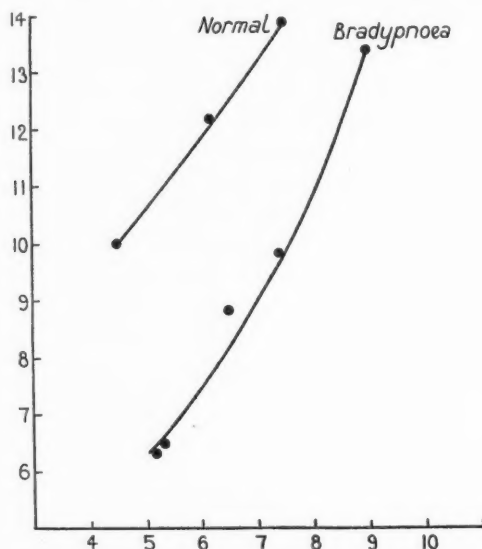
TABLE III
Performance of Work by the Case of Bradypnoea

	During maintenance.	During work.
Minute volume	6,300 c.c.	13,450 c.c.
Tidal air	1,975 c.c.	975 c.c.
Expired air:		
Carbon dioxide	5.21 %	4.93 %
Oxygen	14.74 %	14.42 %
Nitrogen	80.05 %	80.65 %
Respiratory quotient	0.812	0.718
Respiratory rate	3.2 per min.	13.8 per min.
Output of carbon dioxide	328 c.c. per min.	665 c.c. per min.
Intake of oxygen	405 c.c. per min.	927 c.c. per min.

The respiratory rate is increased with work from an average rate of 3.2 per minute during maintenance, i.e. seated at rest on the ergometer, to

13.3 per minute during work. It is apparent that the amplitude of the respiratory excursions tends to decrease with the accelerated rate of breathing. From the figures in the table it is seen that, with the increase in the rate, the tidal air decreases from 1,975 c.c. at rest to 975 c.c. during work, but the minute volume increases from 6.3 to 13.45 litres. The oxygen consumption and carbon-dioxide output within normal limits at rest show a normal increase during work.

The composition of the expired air at rest approaches that of the alveolar air in the normal subject. During work the concentration of carbon dioxide



The effect of breathing mixtures containing high concentrations of carbon dioxide on the minute volume of the case of bradyphnoea. *Ordinates*, minute volume in litres. *Abscissa*, percentage of carbon dioxide.

actually decreases and that of the oxygen rises, though the output per minute of the former and the consumption of the latter increases. This is brought about by the increased pulmonary ventilation. The respiratory quotient, normal at rest, falls during work.

Effects of carbon dioxide. In order to observe the response of the respiratory centre the subject was made to breathe gas mixtures of varying concentrations of carbon dioxide. The gas mixtures were prepared in a large spirometer provided with an electric fan for mixing. Oxygen was added in appropriate amounts to keep the concentration about normal. During the observations the expired air was collected in a Douglas bag and the respiratory movements recorded, so that changes in the rate, tidal air, and minute volume could be determined. In most instances gas mixtures were breathed for five minutes approximately. The changes which were observed in the minute volume of expired air are plotted in the graph. The figures along the abscissa

represent percentages of carbon dioxide in the gas mixture breathed; the ordinates express litres of air expired per minute as dry air at 0° C. and 760 mm. pressure. There is also included a graph which expresses the results obtained from a normal subject of approximately the same height and weight. It is apparent that the response of the respiratory centre as indicated by an increase in the minute volume is quite different in the graphs. The increase is greater in the normal subject than in the case of bradypnoea; e.g. when breathing a mixture containing about 6 per cent. of carbon dioxide the minute volume is nearly 12 litres in the former as compared with 7.5 litres in the latter. This suggests that the respiratory centre in the abnormal subject is less sensitive to carbon dioxide than the normal.

Oxygen want. In Table IV are recorded some results obtained when the subject breathed mixtures containing low concentration of oxygen. With 10 per cent. and 11.5 per cent. of oxygen there was little change in the rate of breathing, but the minute volume was increased moderately. With 7.76 per cent. of oxygen both the rate and minute volume were increased more markedly, the minute volume being over 10 litres. In this experiment the subject became quite cyanosed after 1.7 minutes and atmospheric air was then supplied. The respiratory centre is sensitive to oxygen want but, as in the response to carbon dioxide, the stimulus has to be a strong one.

TABLE IV

Case of Bradypnoea breathing Low Concentrations of Oxygen

Oxygen per cent. in air mixture.	Rate per min.	Minute volume.	Tidal air.
%		litres.	c.c.
20.93	4	5.42	1350
11.5	4.6	7.75	1685
10.05	4.35	6.53	1500
7.76	7	10.35	1492

Discussion

From the observations which have been described it appears that this patient with bradypnoea possesses an indolent respiratory centre. When the subject is at rest and free from emotional stimulation, or is asleep, the respiratory movements are slow and deep. The rate accelerates in response to volitional stimulation, to the excitation associated with speech, to exercise, and, after a fashion, to variations in the tension of carbon dioxide and oxygen in the inspired air. The question naturally arises, what is the nature of this disturbance of respiratory function? In this connexion certain physiological aspects of respiration must be considered.

The respiratory centre, composite in structure and fundamentally automatic in activity, establishes its (anatomical) correlations with the lungs by means of the vagus nerves. It was shown by Hering and Breuer (3), and is still accepted generally by physiologists, that the depth of the respiratory

movements is in part dependent upon the functional integrity of the vagi. According to the degree of inflation or deflation of the pulmonary parenchyma, afferent impulses are transmitted from the lung to the respiratory centres and inhibit the existing respiratory phase with release of the reverse phase. In normal breathing the amplitude of the respiratory movements, never maximal, is limited by these vagal impulses. After section or freezing of the vagi, therefore, the respiratory movements become deeper; but they are also slower. Lumsden (4) believes that this decrease in rate is due to the absence of vagal impulses which tonically accelerate the respiratory centre. These impulses, he believes, arise in vagal endings situated in the mucous membrane of the trachea and bronchi, the stimulus being provided by the passage of air over the ciliated epithelium on these surfaces.

Other views have been advanced by Lumsden and are based on extensive experimental observations regarding the nature of the respiratory centre, more particularly in cats. It is to be remembered that the fundamental element in the respiratory act is inspiration. It is active, in the sense that muscular activity is involved. Expiration, to a large extent, is passive; both acts entail reciprocal inhibition of tone in the muscles concerned with the reverse respiratory phase. It follows that this will apply more particularly to the inhibition of inspiratory tonus during expiration. Lumsden believes that a centre exists in the lower part of the pons, immediately above the level of the *striae acousticae*, which, when liberated from higher control by section through the pons above this level, gives rise to a type of breathing characterized by deep and prolonged inspirations. In the cat, such inspirations may be of 2 or 3 minutes' duration. His records show a gradual diminution in the inspiratory tonus as this phase continues, and then a sudden termination with the onset of expiration. Two or three small and irregular respirations then follow; these are attributed to the anoxaemia which results from the fall in blood-pressure that accompanies the long inspiration. When this anoxaemia is relieved by the small respirations referred to, another long inspiration occurs and the cycle is repeated. This type of respiration in a somewhat modified form is observed normally in certain amphibians which may only breathe once in several minutes. Lumsden calls this the apneustic centre. He adduces evidence to show that the activity of this centre is subordinated to the control of another one situated at a higher level in the pons. It is called the pneumotaxic centre, and it is believed to inhibit, rhythmically, the inspiratory tonus set up by the apneustic centre. Accordingly, with normal correlation between these two centres, the respiratory act resolves itself into the rhythmic development and inhibition of inspiratory tonus. Two other centres, an expiratory and a gasping one, are believed to be situated below the level of the *striae acousticae*.

Certain features which characterize the respirations in the case of bradypnoea may be considered from the standpoint of these conceptions. The slow and deep nature of the respirations is similar, in some respects, to

the breathing in the vagotomized animal, where the respiratory centre is deprived of those afferent impulses which regulate the degree of pulmonary distension (Hering-Breuer reflex) and of those which tonically accelerate the centre (Lumsden).

Attention has been directed previously to the prolonged expiration in this subject. On auscultation over the trachea, an expiratory bruit is heard throughout the whole period; it becomes intermittent, however, especially towards the end stage. Brief pauses occur, but the disturbance in the expiratory act which gives rise to them is not of sufficient magnitude to affect the graphic record of the movements. Since expiration is to a large degree passive in nature, depending upon the inhibition of inspiratory tonus and the gravitational collapse of the thorax, it may well be that this anomalous type of expiration is related to an inadequate degree of inhibition of inspiratory tonus and might be regarded, therefore, as a spurious form of Lumsden's apneustic respiration, arising from altered relationships between the apneustic and pneumotaxic centres.

The possibility of abnormal muscle function has also to be considered. In Parkinsonian rigidity, movements are slow and reciprocal inhibition of antagonistic muscles delayed, and sometimes intermittent as indicated by the cog-wheel nature of the relaxation during passive movements. It is conceivable, therefore, that the delayed inhibition of inspiratory tonus may be muscular in origin and not related to the respiratory centre at all. But there are certain features which are opposed to such a conception. The inspiratory tonus is readily inhibited during volitional hyperpnoea, reflexly during coughing, and also when the subject is speaking or performing work. Moreover, Parkinsonian rigidity disappears entirely or is markedly diminished during sleep. It follows, therefore, that if muscular rigidity accounts for this abnormal type of respiration, it is to be expected that the rate would approach the normal when the rigid state of the muscles was no longer in evidence. As the records show, this does not occur. It may also be pointed out that the rigidity was not very marked in this subject and that, in the large number of cases with extreme grades of muscular rigidity, a similar disturbance in respiration has not been observed.

The occurrence of bradypnoea in a normal subject, as reported by Briggs, raises the question whether or not the slow breathing in this case is related to the epidemic encephalitis at all. The clinical history suggests strongly that there is a relationship. Before his illness the man had been examined for tuberculosis on several occasions and the respirations were apparently normal in rate. No abnormality in the rate of breathing was observed by the individual himself or the relatives before the attack of encephalitis, though they were aware of it subsequently. During the acute stages of the illness he had difficulty in breathing.

We are inclined to regard the bradypnoea as a manifestation of disturbance in the functional activity of the respiratory centre, arising from pathological changes, the result of epidemic encephalitis.

It is a pleasure to express our thanks to Professor Arthur Hall for permitting us to investigate this case and affording us every facility to do so. We also wish to thank Dr. Vincent, Superintendent of the South Yorkshire Mental Hospital, for co-operation on many occasions.

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DESCRIPTIONS OF PLATES

For all figures:—Downstroke = inspiration.
Upstroke = expiration.
Time marker = nine second intervals.
Records read from left to right.

PLATE 21, FIG. 1 A. Bradypnoea: average respiratory rate for 6.75 min., 4.1 per min.; average rate from A-B, 3.8 per min.; average rate from B-C, 5.1 per min.; at B, cough.

FIG. 1 B. Bradypnoea: average respiratory rate for 7.05 min., 3.4 per min. singing National Anthem, repeating Lord's Prayer, and cough (position indicated on chart).

FIG. 1 C. Normal subject: average respiratory rate, 10 per min.

Plate 22, FIG. 2. Bradypnoea: volitional hyperpnoea; average respiratory rate during rapid breathing, 19 per min.; average rate after rapid breathing, 2.3 per min.; note short duration of expiratory phases during the hyperpnoea; kymograph moving more rapidly.

FIG. 3 A. Normal subject, speech: average respiratory rate at rest, 10 per min.; average respiratory rate reading aloud, 12.2 per min.; singing National Anthem, repeating Lord's Prayer (position indicated on chart).

FIG. 3 B. Bradypnoea, speech: average respiratory rate reading aloud, 20 per min.; singing National Anthem, repeating Lord's Prayer, cough, oculo-gyric crises (position indicated on chart).

Plate 23, FIG. 4 A. Bradypnoea, natural sleep: average respiratory rate, 4.5 per min.

FIG. 4 B. Bradypnoea, sleep, $\frac{1}{2}$ hour after omnopon, gr. 1/3: average respiratory rate, 4 per min.

Plate 24, FIG. 4 C. Bradypnoea, sleep, $1\frac{1}{2}$ hours after omnopon: average respiratory rate, 3 per min.

FIG. 5. Bradypnoea, maintenance: seated on ergometer (as shown in chart), average respiratory rate, 3.2 per min.; working on ergometer (as shown in chart), average respiratory rate, 13.3 per min.

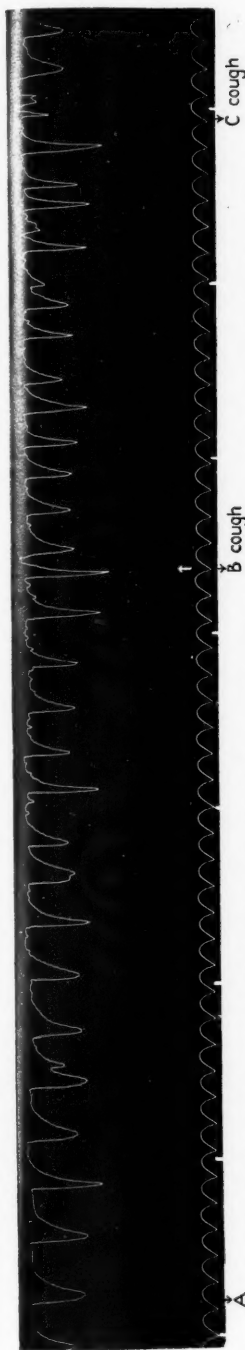


FIG. 1A. Bradypnoea. Average respiratory rate for 6.75 minutes, 4.1 per minute. From A-B, 3.8 per minute; from B-C, 5.1 per minute

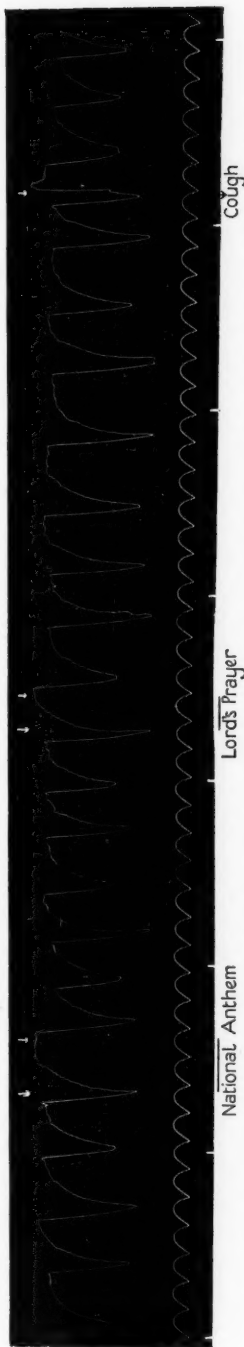


FIG. 1B. Bradypnoea. Downstroke—inspiration. Time marker—9 secs. Average respiratory rate, 3.4 per minute for 7.05 minutes



FIG. 1C. Normal subject. Average rate of respirations, 10 per minute

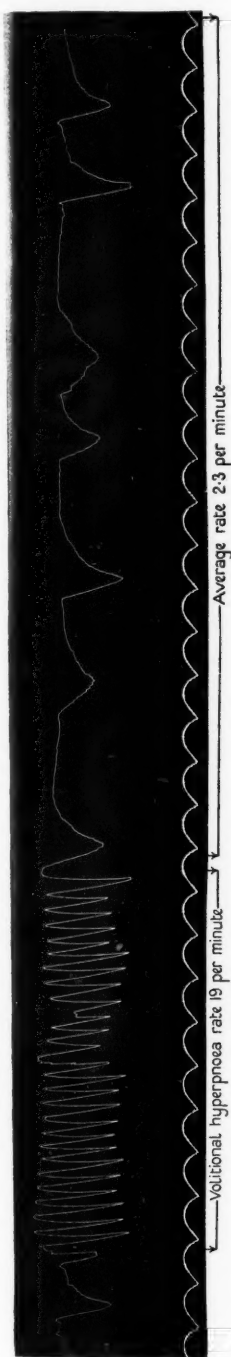


Fig. 2. Bradypnoea. Downstroke—inspiration : upstroke—expiration. Time marker, 9 seconds



Fig. 3 A. Normal subject. Average rate of respirations at rest, 10 per minute. Reading aloud, 12.2 per minute

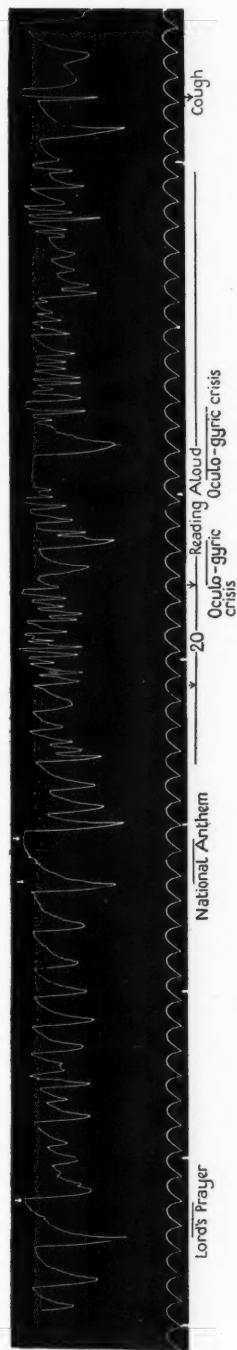


Fig. 3 B. Bradypnoea. Downstroke—inspiration : upstroke—expiration



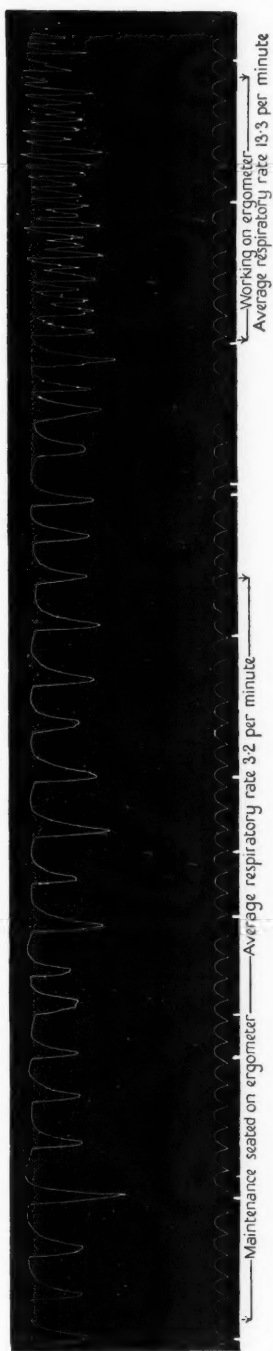
FIG. 4 A. Bradypnoea. In bed: natural sleep. Average rate of respirations, 4.5 per minute



FIG. 4 B. Bradypnoea. Asleep. Half an hour after omnopon grain $\frac{1}{2}$. Average rate of respirations, 4 per minute



Asleep $\frac{1}{2}$ hrs after opium grain $\frac{1}{2}$
FIG. 4 c. Bradypnoea. Average rate of respirations, from A-B, 3 per minute



Working on ergometer
Average respiratory rate 13.3 per minute

Maintenance seated on ergometer—Average respiratory rate 3.2 per minute
FIG. 5. Bradypnoea

THE TREATMENT OF OBESITY¹
A COMPARISON OF THE EFFECTS OF DIET AND OF
THYROID EXTRACT

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THE healthy adult maintains an almost constant body-weight over long periods in spite of considerable variations of physical activity and of food intake. Those who habitually overeat do not necessarily become overweight, nor does a poor appetite always lead to emaciation or physical inactivity. The normal individual undoubtedly possesses considerable flexibility in his metabolism. Food in excess of immediate requirements and not needed to replenish stores can be readily disposed of, being burnt up and dissipated as heat. Did this capacity not exist, obesity would be almost universal, for, as Magnus Levy (1) pointed out, the storage of 200 calories a day would lead to the accumulation of 11 kg. in the course of a year. This small excess might be represented by an extra glass of milk or an extra slice of bread and butter daily. Du Bois (2) calculates that an increase of 10 per cent. on a diet of 2,500 calories would enable an obese individual to store about 10 kg. in the form of fat in the course of a year. Such small excesses are well within the capacity of the ordinary person, but in the obese individual the power of flexibility is much less evident. Why the excess calories should be converted into fat instead of being immediately disposed of has not been satisfactorily explained, but, whatever may be the cause of this disorder, the fact is obvious enough that, since the obese individual continues to add to his stores, his intake of food must be in excess of his daily requirements. Ignorance of the essential causes of the condition handicaps treatment, but clearly, since income exceeds expenditure, rational therapy must consist in correcting the balance. Further storage may be prevented either by cutting down the intake of food or by causing the body to consume more calories. By these measures also it should be possible to use up the stores of fat. Dieting has long been recognized as a successful method of treatment, and many types of régime have been recommended. An increased combustion of food-stuffs can be encouraged in two ways—by raising the general level of metabolism, or by increasing physical effort. Severe and sustained muscular work is necessary if any

¹ Received January 28, 1932.

real increase in the expenditure of calories is to be attained. This will be appreciated when it is recalled that a man of average size only consumes fifty-seven calories extra while walking a mile on the level (3). Unfortunately, those who are considerably overweight find it difficult to increase their movements sufficiently to make much difference to metabolism. On the other hand, where active exercise is possible, there is a danger that the appetite may thereby be increased—a complication to be avoided (4). The other alternative is to employ hormone therapy to influence the activity of the tissue metabolism. Drastic purgation and the encouragement of profuse sweating also result in reduction of weight, but the effects of these are shortlived. The two most practical procedures are, therefore, the use of subcaloric diets and the administration of thyroid extract.

These two methods of treatment have been the subject of special study, and the results obtained in the out-patient clinic have already been reported (5). The present paper deals with observations on a series of in-patients in the metabolic wards of the Royal Infirmary.

The subjects, thirty-five in number, comprise five males and thirty females, whose ages ranged from 14 to 59 years. They included well-marked examples of both exogenous and endogenous obesity, some showing the changes associated with derangement of one or other of the ductless glands, while others could not be classified with certainty (cf. 6). Since no marked difference in results was obvious between the different sub-groups, the series may be considered as a whole. In most of the cases the accumulation of fat had taken place gradually. About half of the patients had been obese for upwards of five years. Two of the males had put on about five stones in a few months. One (No. 8) was a case of pituitary insufficiency who showed genital hypoplasia; the other (No. 25), a young Italian, showed no sign of ductless gland disturbance, but was an enormous eater.

The recorded weights of the patients (59.6 to 178 kg.) show an excess of 15 to 190 per cent. when compared with 'ideal' weights for age, sex, and height. Twenty-five of the cases were more than 50 per cent. over normal standards, and the average for the series was 69 per cent. One case (No. 1), an example of hypopituitarism who was undergoing reducing treatment for the relief of an arthritis of the knees, was only 5 per cent. overweight when examined.

Construction of diets for reduction. Certain physiological principles must be attended to in planning diets for obesity. Consideration has to be given not only to the total number of calories provided, but also to the proportions of the basic food-stuffs, carbohydrate, protein, and fat. Most published diets which are in general use yield from 1,100 to 1,500 calories, but some more recent ones, notably those of Mason (7) and of Evans and Strang (4, 8), yield as little as 300 to 600.

In deciding the quantity of fat to be allowed it is assumed that, as the body will call upon its own stores, this substance can be reduced to a minimum in the diet. Some régimes allow no added fats, the patients

merely getting fat which is inseparable from the other foods, such as meat, and in consequence the daily intake of fat may be as low as 9 gm. To compensate for the absence of fat-soluble vitamins special concentrated preparations have to be added. Carbohydrates are usually restricted as far as possible, since they are known to be the principal source of surplus energy in the obese. Sufficient carbohydrate must be retained, however, to prevent the patients feeling unduly weak and in order to avoid the occurrence of acidosis. Carbohydrates are the most powerful spacers of protein, and their too severe restriction leads to excessive loss of body nitrogen. The question of the most desirable value for protein is more difficult to settle. Because of its stimulating action on metabolism, protein is often given in large quantity (e.g. Banting and Salisbury diets), but, as this means a higher caloric intake, its advantage is somewhat doubtful. If the protein of the diet is too low a negative nitrogen balance will result from an excessive destruction of tissue proteins. The optimum intake of protein is usually put at about 1 gm. per kilo body-weight, though whether the 'ideal' or the actual weight should be the guide is not clear. The standard 1,000 calorie diet supplied to the subjects of this study yielded from 0.8 to 1.4 gm. per kilo body-weight. The older idea that limitation of fluids favours metabolic activity has been given up, and no restriction is now placed on the intake of fluids.

In this investigation a large number of different diets have been tried, the caloric values ranging from 2,700 to 800. The patient on first coming under observation was usually given a diet similar to that taken at home. From the dietary history of the patients it was learnt that most of them were accustomed to take badly-balanced diets, consisting largely of starchy foods and fats with a minimum of animal proteins and vegetables. On admission to hospital the patients were invited to select their own foods, but it is doubtful if the choice approximated their accustomed fare, as it usually included more vegetable and meat, and was altogether better than that taken at home. The caloric value of the initial diets also was probably less than that of the usual intake, as a greater proportion of bulky foods was taken in hospital. In order to facilitate comparisons, all the patients were put for a time on a standard reducing diet of 1,000 calories which contained carbohydrate 100 gm., protein 60 gm., fat 40 gm., and this diet was also usually employed when thyroid was subsequently given. During part of the investigation other diets were also tried in order to obtain information regarding the value of the various food substances. Experience showed that in order to see the effect of a diet it was necessary to continue it for at least seven days, and few of the periods were under ten days. The influence of a previous level of protein intake is still felt for four or five days after it has been changed (9), and study of diabetics has shown that something similar is true of carbohydrates.

Results. The low calorie diets were well borne. After the first day or two hunger was not complained of, and there was no evidence of weakness or

ready exhaustion (8, 10). Indeed, the patients soon claimed that they felt better, and many minor symptoms disappeared (8). Sometimes constipation required attention.

The most marked result of the treatment was reduction in weight. Without exception, *all* the subjects lost weight while on the subcaloric diets, some more readily than others. This is equally true of the most marked endocrine cases.

The higher diets during the preliminary period usually varied from 1,700 to 2,700 calories. On these diets it was hoped that the patients would be able to maintain weight, and so give an idea of their usual intake. This object was not realized, for while only one kept her weight (No. 17) and two (Nos. 1 and 12) made a slight gain (total 75 gm. and 40 gm.), all the others declined. The average loss on the higher diets was 157 gm. (range 43 to 400 gm.), which is equivalent to 0.14 per cent. of the body-weight. An explanation for this loss of weight may be found in Table I.

TABLE I

Relation of Food Intake to Weight-loss

		<i>Initial Diets.</i>									
		Over 100 %	90 % +	80 % +	70 % +	60 % +	50 % +	40 % +			
No. of cases		2	4	4	7	7	4	4			
Average weight change		+58 grm.	-64	-148	-183	-186	-152	-278			
		<i>1,000 Calorie Diet.</i>									
		70 %	65 %	60 %	55 %	50 %	45 %	40 %	35 %	30 %	25 %
No. of cases		1	—	1	2	3	6	8	14	2	1
Average weight-loss		-20	—	-155	-113	-122	-122	-169	-219	-207	-243
		<i>1,000 Calorie Diet and Thyroid.</i>									
No. of cases		1	1	—	1	1	—	5	11	6	2
Average weight-loss		-190	-275	—	-220	-213	—	-257	-260	-332	-460

The percentage figures in the above table represent the proportion of the estimated total calories required, which was actually supplied by the diet consumed.

The caloric requirements for a day can be estimated by adding a proportion to the calories used during the basal period. For an ordinary quiet life an allowance of 50 per cent. is usually made, while, for patients in hospital, values of 20 to 40 per cent. have been suggested (8, 11, 12, 13). In Table I the value of the food consumed is shown as a percentage of the estimated caloric requirement, and the average loss of weight is compared with this. It will be seen that during the initial dietary period the patients who gained weight were receiving more than their estimated needs, while a loss occurs when 90 per cent. or less of the estimated calories is supplied by the food. This would seem to justify the acceptance of an allowance of 50 per cent. over basal calories as an approximation to the real total calories for the day. In the remaining subjects the loss of weight bears a direct

relation to the sufficiency of the diet. On the 1,000 calorie diets the average loss was 172 gm. per day (range 82 to 330 gm.). This represents a daily loss of 0.17 per cent. of the body-weight. The higher initial diets on the average supplied 77.1 per cent. of the required calories, while the 1,000 calorie diets only gave 39.5 per cent. of the body needs. In view of this, and considering that the average of the higher diets is about 2,000 calories, it is remarkable that there is not a greater difference between the amount lost on the two diets. An explanation of this will be offered later. The patients who took a diet of 800 calories lost 200 gm. daily on this, in contrast to 181 gm. for the same cases on the 1,000 level.

Several subjects temporarily received still lower diets during *non-febrile* upsets due to pain, nausea, &c. A reduction of intake from 300 to 500 calories causes a sudden loss in weight, which is usually rapidly made up as soon as the higher diet is restored. For example, Case 14, who had been steadily losing 200 gm. daily, developed abdominal pain and was only able to take 390 calories. An immediate loss of 1,400 gm. took place on the first day, and this was followed by a rise of 400 gm. in four days. Sudden changes of such magnitude cannot depend solely on combustion of body stores. A change from a lower to a higher diet was usually accompanied by an arrest in fall, or by a slight rise in weight. The results obtained on the regular subcaloric diets demonstrate the great importance of the actual caloric value of the food intake.

The rate of weight-loss from day to day was usually fairly uniform, but for days at a time irregularities of 100 to 300 gm. were sometimes seen under apparently uniform conditions. Such daily fluctuations are of little importance, though they occasionally make it difficult to ascertain the real rate of loss over short periods, and this emphasizes the importance of only making observations on periods of adequate length. Some of these fluctuations may depend on incomplete evacuation of urine or faeces, though precautions to avoid this were taken. Changes in water storage have also been suggested as an explanation (3). In addition to these daily variations a disturbance was also found to accompany menstruation. For two or three days before the period weight-loss usually ceased, and a gain of as much as 1,000 gm. might occur. This was followed about the middle of the period by an increased rate of loss in weight.

The reduction of weight on a subcaloric diet of constant character tends to slow down after a time, until eventually all loss may cease. This tendency is well recognized (14), and Luciani (15) has suggested a hyperbolic formula as a mathematical expression of the phenomenon. As an illustration of this slowing the findings in Case 25 may be cited. This patient remained for twenty-one days on a constant dietary intake of 1,200 calories, and the average daily loss for the whole period was 260 gm. During the first week the rate was 457 gm. a day, in the second 214 gm., while for the last week the daily loss was only 157 gm.

The influence of a subcaloric diet falls naturally into three stages. During

an initial period of a few days there is a rapid change of weight which has been attributed to dumping of water stores (4, 16). Then follows a steady but diminishing loss proportionate to the size of the diet. Lastly, there may occur a phase of weight maintenance at a new level. Several explanations may be offered for this decrease in the rate of weight-loss. Removal of body water may play a part in the earlier stages, but cessation of this will not explain the later flattening of the curve. It has been suggested that it is a conservative mechanism preventing undue loss of body stores. In part it may depend on the altering relationship of food intake to the body needs, for as the weight falls the total caloric requirements also diminish, and the discrepancy or deficit between these and the food supplied constantly becomes less. To some extent the phenomenon is due to a reduction in the metabolic rate (*infra*). Weight maintenance or even gain over a few days may depend on water retention (3), and it is pointed out that 100 gm. of fat on oxidation yields a greater weight of water (107 gm.). Grafe (17) reports a patient who kept her weight practically steady for twenty-two days, though receiving an inadequate diet of 1,000 calories. The ability of certain patients to maintain their weight at a new level in spite of low caloric intake has caused certain writers to suggest that the obese are not subject to the ordinary metabolic laws (18).

TABLE II

Effect of Different 1,000 Calorie Diets on Weight-loss

Diet.	C.	G.	6 cases loss. gm.	2 cases loss. gm.	2 cases loss. gm.	4 cases loss. gm.	Total cases.	
							No.	Average loss. gm.
Standard 1,000 calories	100	140	157	275	169	160	14	181
Low C., high F.	40	70	219	200	—	—	8	205
Low C., high P.	40	100	216	—	178	146	12	183
High C., low P.	120	147	—	—	122	—	2	122
High C., low F.	120	206	—	49	—	—	2	49
Average for all 1,000 calories	—	—	167	190	160	117	14	145

The total figures in the last column are not strictly comparable as they refer to different numbers of cases. The values recorded in the other columns are the average losses on different diets, and comparison can only be made between the figures in one column.

Effect of different food-stuffs. Fourteen patients were given 1,000 calorie diets of different composition in order to discover the importance of the various food-stuffs. As each dietary period lasted from seven to ten days it was not possible to try all the diets on every patient, but usually only three at most. The order in which the various diets were given may influence the results owing to the tendency for the rate of weight-loss to diminish as time advances. For this reason the sequence of the diets was changed in different subjects, except that the standard diet was always given first. Table II can only be regarded as a rough indication of the probable value

of the factors, because of the small number of observations and on account of the great individual differences recorded. (Compare in the different columns the amount of loss on the standard diet!) The most striking feature of the table is that the losses appear to be inversely proportionate to the carbohydrate content of the food. Where the carbohydrate intake is low the rate of loss in weight is greater and conversely (19). The effect of the protein level is not very clear, but it might be suggested that the 'G' value (total available carbohydrate including that formed from protein) might be more important than the simple carbohydrate figure. The results are in accordance with previously recorded findings (13, 20). The records show that a change from a low carbohydrate diet to one which contained a greater amount may be often followed for a few days by an arrest of loss, or even by a temporary gain in weight. This is explained (1) by the tendency to retain water on a carbohydrate diet and to give it out on a rich fat diet. The influence of protein was further studied in one patient (No. 25), who took the Salisbury diet during several periods. The subject was a youth of 14, enormously overweight, but showing no sign of endocrine disturbance. He was an exceedingly gross eater, who consumed large quantities of fatty foods and carbohydrate. On the initial diet of 2,150 calories he lost weight at the rate of 314 grm. a day, then for twenty-one days on 1,200 calories the loss was 260 grm. daily. The first Salisbury period was for four days. On transferring to this régime he abruptly lost 1,400 grm. during two days, and then during the next two days gained 500 grm. Between the special test periods the patient consumed the ordinary standard 1,000 calorie diet. The results during the second Salisbury period were similar to those on the first. The third Salisbury period lasted for six days, and for the first two of these he lost 800 grm. a day. Then following this the weight remained constant for six days. In none of the Salisbury periods was the great initial fall kept up. This failure may in part be attributed to the fact that this diet yielded 2,350 calories. After a fourth similar period of Salisbury the patient was put for six days on a mixed diet of the same caloric value (C. 234, P. 152, F. 89), and this caused a gain of 900 grm. The Salisbury régime was not well borne. It is an unappetizing diet, and difficulty was experienced in persuading the subject to continue it. On it the patient felt lazy and even drowsy, and he complained of a heavy headache. Constipation was troublesome in spite of the large quantities of water consumed, and actual sickness occurred once. The sudden and marked initial fall cannot be due to the high protein, since the effect was not kept up after the first two days.

Effect of thyroid extract. Established as a remedy for myxoedema in 1891, thyroid extract was soon tried in other conditions. Its first employment for obesity has been attributed to Dr. Barron of Liverpool (21). Since that time its popularity has waxed and waned. Formerly, large doses were given, but, as the limits and dangers have become recognized, more conservative tendencies now prevail. Most modern writers warn against its

promiscuous use in obesity, and some consider it irrational, dangerous, and totally unjustified, since it may induce a degree of hyperthyroidism (22). While theoretically this may be true, this extreme view is much too narrow. There is no doubt that many obese patients can be quite satisfactorily treated by careful attention to the diet, and for these the drug is quite unnecessary. There are others in whom dieting alone is insufficient, at least for a time. Where there is definite subthyroidism, or when the weight has become stabilized at a new level on a subcaloric diet, thyroid extract is undoubtedly of service. It is a useful agent if properly handled, and when definitely indicated is invaluable. To regard it as a pleasant substitute for dieting which will allow the patient to continue his ordinary habits of feeding is entirely unwarranted (4). Intolerance to thyroid has been seen occasionally in the out-patient clinic, but none of the patients specially studied developed any untoward symptom from its use. The dose employed has been controlled by watching the pulse-rate, the drug being discontinued when the pulse reached 100 per minute. This critical level was only reached in a few of the patients. The average advance in pulse-rate was between ten and twenty beats. Little effect was noticed in the temperature, a rise of about half a degree being sometimes seen. Although the basal metabolic rate was frequently taken, it was never considered necessary to alter the dose of the thyroid because of the increased metabolism.

TABLE III

Relation of Weight-loss to Dose of Thyroid

	Diet only.	Thyroid, grains.					Average when on thyroid.
		3 gr.	6 gr.	9 gr.	12 gr.	15 gr.	
No. of cases	27	22	19	17	11	4	27
Observed loss	162 grm.	219	245	304	398	412	273
Calculated loss	157 "	210	263	316	369	422	—

When thyroid is given its effects are not at once apparent. Two or three days usually elapse before any change is evident. Nine cases showed an increased rate of fall from the first day of thyroid, while in three there was no increase until after five days. The daily dose of thyroid extract was kept constant for seven to ten days so as to allow the full effect to be observed before an increase was tried. Most of the patients began with 3 gr. a day, and then took 6 or 9 gr. A certain number advanced to 12 or 15 gr., and two received 18 gr. for a time. While the doses were usually given in ascending order, this was not always so, for the thyroid had sometimes to be discontinued or a smaller dose substituted. Twenty-four patients received the standard 1,000 calorie diet during the trial of thyroid, while three cases were kept on the higher diets which they had been taking for some time previously. The average daily loss of weight during the thyroid periods was 273 grm., compared with 162 grm. *for the same cases* on diet only. The range of weight-loss for the whole thyroid period was from 141 to 500 grm. daily, eight of the cases showing figures of 300 and upwards.

These represent a loss of 0.3 per cent. of body-weight daily, as compared with 0.17 per cent. for diet only. On commencing thyroid no sudden and considerable reduction occurred, such as was seen for the first day or two after a diet of lower calories was given.

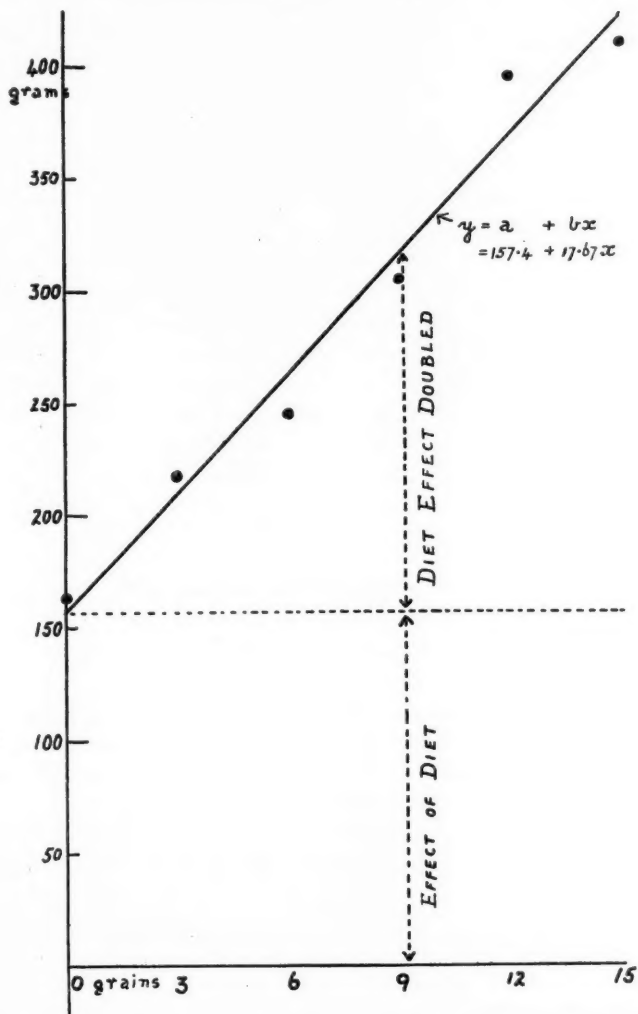


FIG. 1. *Effect of different amounts of thyroid.* Base line represents dose of thyroid in grains; ordinates average loss of body-weight in grams. Observed results shown as dots, calculated figures as straight line. Note that 9 gr. of thyroid extract are required to double the effect due to 1,000 calorie diet alone.

The effects of different quantities of thyroid extract are summarized in Table III. It will be seen that each addition to the dose led to an increased rate of weight-loss, and that the increase was fairly uniform. From the

figures available the best values have been calculated by the method of least squares. The agreement with the observed results is fairly close, as will be seen from the accompanying figure (Fig. 1). Each grain (0.06 grm.) of extract produced on the average 17.67 grm. of additional loss in weight. It will be noticed that no less than 9 gr. of thyroid are necessary to equal the effect of the 1,000 calorie diet alone. This is a quantity which many obese subjects are unable to tolerate. When administration of thyroid was discontinued its effect often persisted for a few days, but this was usually followed by a period during which a decided slowing in the weight-loss occurred. This is shown in Table IV.

TABLE IV
Loss of Weight in Grams in Different Periods

Case No.	Diet only.	On thyroid.	Off thyroid.
	Daily weight-loss. grm.	Daily weight-loss. grm.	Daily weight-loss. grm.
2	135	252	150
4	143	251	133
8	176	366	63
12	190	221	130
20	—	225	75
22	156	235	200
30	264	357	110
32	246	257	65
33	261	319	200
34	189	490	400

As the dose of thyroid was usually varied at intervals it was not possible to ascertain definitely whether the effect tends to diminish as time advances. Case 20, taking a diet of 2,000 calories, received 5 gr. of thyroid daily for forty-eight days. Two different preparations, C and E, were employed in the following order, and produced a daily loss of C 412 grm., E 300 grm., C 131 grm., E 190 grm., C 150 grm. These figures suggest that thyroid produces less effect after a time, but it must be remembered that the fall in rate of weight-loss also includes the adjustment to the diet.

Effect on basal metabolism. Most observers have found that in obese individuals the basal metabolic rate lies within normal limits (23, 24, 25).

TABLE V

B.M.R.	Below -20 %.	-11 % to -19 %.	-1 % to -10 %.	Normal.	+1 % to +10 %.	Over +10 %.	Total.
No. of cases	1	7	16	1	6	2	33

When first examined the majority of the subjects lay within the limits ± 10 per cent. (average -6.7 per cent.) though the bulk of them were on the lower side of normality. A quarter of the number were definitely sub-normal, and two showed unusually high values. The usual method of calculating the metabolic rate on the basis of the surface area assumes a normal ratio between the active and the inert tissues of the body. Because of the greater proportion of inactive fat in the obese the results must be somewhat

fallacious. In reality the metabolism in such subjects is much more active than these figures suggest. The fact that the overweight individual has a metabolism approximately of normal rate, in proportion to the surface area, implies that he is actually using up a much greater amount of energy than would a healthy person of 'ideal' weight of the same height and sex. If the theoretical figures derived from the greater surface area of the obese is compared with those of the 'ideal' normals of corresponding age, sex, and height, it is found that the thirty-five overweight cases would consume in the average 24.9 per cent. more energy (8). This excess metabolism would in other cases raise a suspicion of hyperthyroidism (22, 26). But, since the majority of the patients had a metabolic rate below normal, the actual excess is not so great. Actually six of the cases, in spite of their greater surface area, were found to be using an average of 9.5 per cent. less energy than the corresponding normals. These figures are arresting in view of the generally accepted belief that the metabolism in the obese is carried on at a low level, and they also cast grave doubts on the statement that such cases eat sparingly. This view is also supported by the marked loss of weight which occurred on the initial diets. An actual example may serve to make the position more clear. Take for instance No. 20, a female aged 43, 155 cm. in height, who ought to have a normal surface area of 1.58 sq. m. and a basal consumption of 1,360 calories, but being 103 per cent. overweight her surface area was 1.99 sq. m. (26 per cent. in excess), which would demand 1,720 calories. Actually, however, having a B.M.R. of 94 per cent. normal, she was found to be using 1,616 calories (a figure only 19 per cent. over the 'ideal' normal).

After a period on the low calorie diets the basal metabolic rate invariably fell to a lower level. This phenomenon occurs during complete fasting, and there are many references to it in the literature. Benedict's subject L., for example (14), went for thirty-one days without food, and during the first thirteen days his metabolism gradually fell to 63 per cent. of its original value, thereafter remaining constant. It is important to note that there was an absolute reduction in rate per square metre, and greater than would have been expected from the mere reduction in body surface. The same thing has been shown in *healthy* individuals while on a subcaloric diet. In Benedict's squad A of thirteen normal men (3) there was a reduction of total metabolism of 15 per cent. to 20 per cent., the metabolism of his subject Gul, for example, falling from 103 to 87.

For twenty-one of the subjects in this series the average metabolism while on the initial diet was 98 per cent., but after three weeks on lower diets this value had fallen to 85 per cent. Thereafter the metabolic rate remained practically constant while the subject continued the same diet. The reduction in metabolic activity was not accompanied by any obvious change in the patient's activities. This fall in the basal metabolic rate has been regarded as a conservative mechanism or as being due to a decrease in cell activity consequent on the lower intake of protein in the

diet. It should also be observed that as the body-weight declines the demands on the musculature will be less. The lower rate of metabolism may explain in part the tendency for the rate of fall in weight to decline steadily and to come to a constant level. This slowing of metabolism is an unavoidable disadvantage when attempting to effect weight reduction by means of a subcaloric diet alone. To counteract it the use of alternate periods of low and higher diets has been suggested (27) and this plan may tend to keep the metabolism at a higher level.

The administration of thyroid extract raised the *average* basal metabolism in twenty-three cases to 111.8 per cent., a figure which should be compared with 95.4 per cent. for the initial high diets, and 90.3 per cent. for all the 1,000 calorie diets. The amount of increase varied considerably according to the level of the first reading, the amount of thyroid, and the length of time for which it was given. Of the twenty-four cases receiving thyroid four remained under 100 per cent. and four were raised to over 120 per cent. without any ill effects being apparent.

The *respiratory quotient* was not significantly altered while the patient was on thyroid.

Acetone was regularly looked for in the examination of the urine. It never occurred except in traces, and then only in a few cases. Its occurrence was to be explained by an exceptionally low intake of carbohydrate (under 40 grm.), or when the patient was for some reason unable to take more than about 400 calories per day. This relative absence of acetone is in keeping with the findings in fat diabetics, who seldom show ketosis even under conditions which would lead to considerable excretion of acetone bodies in non-obese cases (27, 28).

TABLE VI
Nitrogen Balance

Initial Diet.			Standard 1,000.			Low CHO.		
No. of cases.	Food N.	Urine N.	No. of cases.	Food N.	Urine N.	No. of cases.	Food N.	Urine N.
	grm.	grm.		grm.	grm.		grm.	grm.
16	11.13	7.88	17	10.04	8.65	—	—	—
—	—	—	11	9.94	9.22	—	—	—
—	—	—	4	9.60	9.56	4	14.30	12.05
High CHO.			800 Cals.			Thyroid period.		
No. of cases.	Food N.	Urine N.	No. of cases.	Food N.	Urine N.	No. of cases.	Food N.	Urine N.
	grm.	grm.		grm.	grm.		grm.	grm.
—	—	—	4	10.16	9.10	16	10.37	10.10
—	—	—	—	—	—	11	9.94	10.84
4	8.53	7.09	—	—	—	—	—	—

Since the cases did not all have the different diets the total figures in the top line are not strictly comparable. Special figures for eleven of the cases on standard diet are given for comparison with the thyroid results, and for four subjects who also had the high and the low carbohydrate diets.

Nitrogen balance. On the initial higher diets which contained from 55–95 grm. protein, the output of urinary nitrogen was always less than the intake. The standard 1,000 calorie diet contained 60 grm. protein, and with this intake the average urinary nitrogen was a little greater than on the higher diet. If an addition of 1 grm. nitrogen is made for loss in the faeces, nine of the seventeen cases showed a slight negative balance, but in no instance was it significant. The high and the low carbohydrate diets (with P 40 and P 120 respectively) show the tendency of the urinary nitrogen to follow the character of the intake. During the thyroid period the output of nitrogen was somewhat raised. Allowing for faecal nitrogen, nine of the sixteen cases were in negative balance. The influence of the thyroid can best be judged by comparing the results in the eleven cases for whom comparative standard diet figures are available. It will be seen that during the administration of thyroid an extra 1.62 grm. is lost from the body. It is possible that the extra loss in part represents the breaking down of protein tissues (e.g. muscle) no longer required as the body-weight decreases. The necessity for maintaining the nitrogen balance in such cases has been questioned by Mason (22).

Specific dynamic action of food. When a normal individual ingests food his metabolic rate is raised above the basal level for some hours. The extra heat production due to this is said, in the case of a mixed meal, to be about 6 per cent. to 10 per cent. of the caloric value of the food taken. Protein substances have a much greater stimulating effect (30 per cent. to 75 per cent.) than carbohydrates (6 per cent. to 20 per cent.), or fats (2 per cent. to 6 per cent.).

Great difficulties confront those who attempt to estimate the specific dynamic action with ordinary laboratory equipment, and it is doubtful whether much reliance can be placed on *any* published clinical data. The methods employed vary considerably and there are great differences in the results reported. The findings may be shown in two entirely different ways, either by noting the maximum rise of the metabolic rate over the basal value or by calculating the total 'extra' calories as a fraction of the value of the food consumed. In either case the result depends upon the correctness of the initial basal reading and, as the experimental errors in clinical calorimetry are at least ± 5 per cent., the final figures cannot be very accurate. For example, if the real B.M.R. was -5 per cent., the actual reading obtained might be anything from 90 to 100, and for a maximum of 120 the estimate might be anything from 115 to 125, so that the increase to be attributed to specific dynamic action would vary from 15 to 35 points, according to which figures were obtained. Some of the difficulties involved are discussed by Strang and McClugage (29). It has been claimed that a low specific dynamic action, particularly of protein, plays a large part in the production of obesity, while others have found that the obese react to food exactly as normals do. This question has been studied in twenty-five of the patients in this series. Test meals were given during the

different diet periods and when the patients were taking thyroid. The effect of different food-stuffs was tried by giving, on successive days, 50 gm. glucose, 50 gm. meat protein, and 50 gm. fat in the form of cream. The subjects were prepared as usual for estimation of the B.M.R., and after taking the test breakfast they remained at rest for three or four hours. Two separate basal samples were taken in order to obtain greater accuracy, and further samples of expired air were collected at the end of each half-hour.

TABLE VII

*Specific Dynamic Action of Food**Percentage Increase in Metabolic Rate over Basal*

	Carb. Meal.		Prot. Meal.		Fat Meal.	
	No. of cases.	M.R. increase.	No. of cases.	M.R. increase.	No. of cases.	M.R. increase.
All cases on diet	21	+ 18 %	25	+ 18 %	13	+ 11 %
Cases before thyroid	8	+ 19 %	8	+ 19 %	7	+ 9 %
Cases receiving thyroid	8	+ 16 %	8	+ 23 %	7	+ 17 %
Controls—thin subjects	6	+ 18 %	6	+ 31 %	6	+ 15 %

The figures in Table, VII show the average *maximum* increase following the ingestion of food as a percentage of the original metabolic rate. Individual cases showed very wide differences—their responses ranging from 3 per cent. to 44 per cent. The data obtained could not be correlated with other observations and were of no service in classifying the cases. Records from six abnormally thin subjects are shown for comparison. The only striking contrast is the difference in the figures for protein. Although the basal figures are increased during the thyroid period the *percentage* increase after the same test meals is of the same order. The effect of thyroid has been to increase slightly the specific dynamic action of protein and fat, while the figure for carbohydrate is somewhat reduced.

It is interesting to note that the increased heat production which follows feeding appears to bear a relation to the initial value of the metabolism, being greater when the basal metabolic rate is low. This is shown for the protein test meal in Fig. 2.

Water exchange. It has not been possible to carry out a complete investigation of the water balance, but a record of the intake of fluid and output of urine has been kept. A comparison of these, 'while capable of 100 per cent. error, yet yields information of clinical value' (2). As is natural, individual patients showed considerable differences, and this fact necessitates that special care be taken in comparing the figures. Records for the three main periods are available for twelve cases. It will be noticed that when the patients are on the 1,000 calorie diet their intake of fluid is less than on the higher diets (30), in spite of the fact that the solid foods of the latter contained more water and also yielded more on combustion. It may be that on the subcaloric diets the deficit is made up from the water derived from combustion of tissue fats (107 c.c. from 100 gm. fat). The

output of urine varies in the opposite direction, being greater on the lower diets. These changes were shown by all but three of the cases.

The figures for the thyroid period should be compared with those for the 1,000 calorie diet. It will be seen that the effect of the thyroid is to increase both the intake and the output of fluid. The average urinary

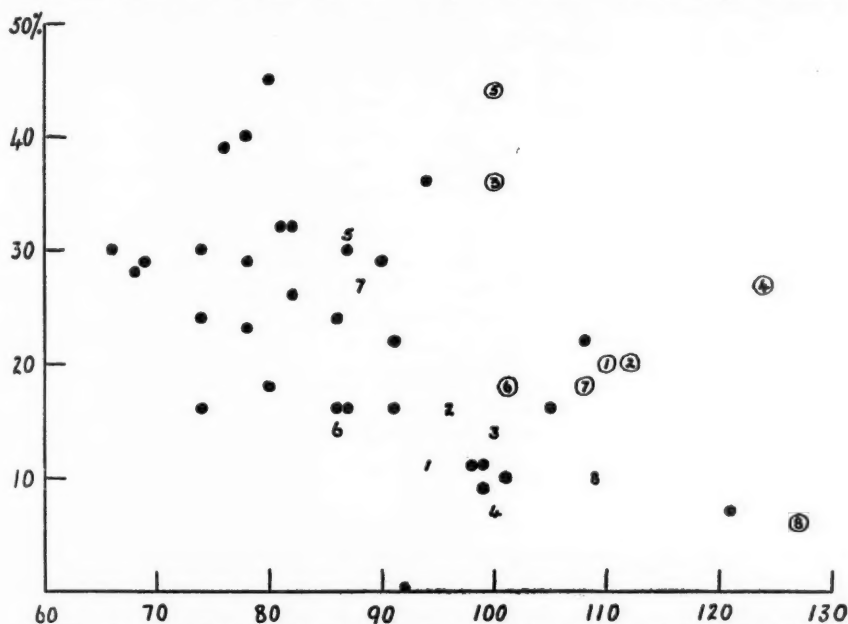


FIG. 2. *Specific dynamic action of protein.* Abscissae represent the initial B.M.R. values—100 being normal. Ordinates show the maximum percentage increase of metabolism after the protein test meal. The figures surrounded by a ring were found when the patients were taking thyroid and should be compared with the unringed figures which refer to the same cases on diet only.

output is very close in the two cases, but no fewer than nine of the twelve patients showed a difference of more than 100 c.c. The differences were more marked on the higher doses of thyroid. The greater intake of fluid under the administration of thyroid is probably related to the higher metabolism and to an increased evaporation from the skin.

TABLE VIII

Period.	No. of cases.	Fluid drunk.	Urine.	Difference.
High diet	12	1814	1041	773
1,000 cals. diet		1675	1205	470
Thyroid		1776	1244	532
Standard 1,000	4	1420	1045	375
Low CHO. 1,000		1461	1106	355
High CHO. 1,000		1354	942	412

Substances involved in loss of weight. The limited character of the examinations makes an exact analysis of this question impossible, but enough

information is available to afford an interesting comparison. A superficial inspection shows that it is unlikely that the loss of weight is due to fat alone. A temporary fall in weight of as much as 500-1,300 grm. might occur in one day. Since such a loss was not due to the elimination of retained faeces or urine, some other explanation must be sought. If a fall in weight of this extent was due to fat alone, it would require the expenditure of 4,500 to 11,700 calories in addition to those derived from the food—a quantity impossible to deal with. In the same way the sudden and considerable gains in body-weight cannot be due to fat storage.

Loss in body-weight may include the disappearance of glycogen, protein, fat, or water. That glycogen plays any great part is unlikely, for the whole amount of this substance in the body is very small and, as Du Bois points out, if used alone would only be able to maintain metabolism for two days (2). In the complete fast observed by Benedict (14) the subject lost a little glycogen during the first three days, then for the next ten days only traces, and thereafter none, the remainder being conserved by the body. Wiley and Newburgh (31) assume that after a few days on a new subcaloric diet the utilization of carbohydrate matches the intake.

As most of the observations during the periods on 1,000 calorie diets showed that the patients were in nitrogen balance, wastage of body protein is out of the question. The loss of weight, must, therefore, represent removal of fat and water.

During the initial days of complete fasting (14, 16) large losses in weight are always observed and similar changes are found on moderate restriction of food (3). These are usually attributed in part to removal of preformed water from the tissues. The preformed water of the body consists of two components—(a) that more or less fixed to protein and glycogen, and (b) a free residuum. It is usually assumed that protein attaches three (32) or four (1) times its weight of water. The degree of hydration of glycogen is not known.

TABLE IX

Initial Weight-loss in 27 Cases

	Average for period.	1st day.	2nd day.	3rd day.	4th day.	5th day.	6th day.	Average for 6 days.
	grm.							
On high diets	180	420	210	166	152	74	192	202
On 1,000 cals.	174	316	339	266	205	261	191	230
Thyroid period	269	263	306	226	240	262	333	272

Average figures for weight-loss on each of the first six days in the three principal periods are given in Table IX together with the averages for the whole period and for the six days. On the 1,000 calorie diet the initial loss is found to be considerably in excess of the average for the period, especially during the first three days. About half of the cases showed a loss of more than double the average for the whole period. The numbers who gained weight on any of these days are very small. The data for the

period of high diets are similar. In about 20 per cent. of the initial observations the loss of weight in one day exceeded 500 grm.

At the commencement of the thyroid periods no increased loss is evident in the average figures, as in the case of an alteration of the dietary intake. In spite of this a loss of over 500 grm. was found in 33 out of 162 observations.

The large loss of weight which occurs when the patient is unable to take food for a day is of the same nature. This phenomenon may depend on the lower carbohydrate intake and a consequent adjustment of the body glycogen. It would appear that after about the third day this factor is of less importance and the reduction of weight on the lower diets is probably due to loss of fat and water from the body. An attempt has been made to find the relative proportions of these indirectly.

A balance sheet can be drawn up comparing the estimated heat production derived from the observed basal metabolic rate with the calories available from the food and from the tissues, the latter being calculated from the weight-loss. The observed basal calories obtained by analysis of the expired air gives a measure of the metabolism during complete rest, and to this must be added a percentage to allow for various other activities. The addition suggested for a subject in bed or living a quiet sedentary life varies from 20 per cent. to 50 per cent. Benedict and Carpenter (13) allow 36 per cent. for wakefulness and sitting, and 60 per cent. for standing. As a first approximation 50 per cent. might be added to the observed basal calories, and in the following discussion this estimate will be referred to as the 'metabolic calorie value'.

It has been shown above that the reduction in weight is not entirely due to disappearance of fat. The figure for weight-loss must, therefore, be multiplied by some factor before it can be converted into calories. During the period of undernutrition it is the fat depots which are most affected, but these do not consist of fat only. An analysis of two samples of fatty tissue obtained post-mortem gave the following values:—

TABLE X

	Fat.	Water.	Residue.
Subcutaneous fatty tissue	80.0 %	17.3 %	2.7 %
Omental fatty tissue	86.1 %	12.4 %	1.5 %

Bozenraad (33) quotes other authors as finding from 15 per cent. to 30 per cent. of water in fatty tissues, and himself in a series of analyses found from 7 per cent. to 46 per cent. His figures for abdominal fat in obese subjects are 10, 13, 13.5, and 17 per cent. Lauter (34) found about 10 per cent. of water in subcutaneous fat, and Benedict assumes a similar value. Bischoff (35), on the other hand, reports 29 per cent. in one case. Evans and Strang (8) believe that the fatty tissues of the obese have a great capacity for storing water (though other observers have shown that there is a much greater proportion of water in the fat of emaciated subjects (33)).

These observations would warrant the arbitrary use of the figures 20 per cent. for water and 80 per cent. for fat in drawing up a balance sheet, such as is shown herewith. The estimate obtained by adding together the value of the food and the figure derived from the weight-loss will be referred to as the 'weight-loss calories'.

TABLE XI

Treatment—Diet only

J. M., female, aged 41, height 5 ft. 3 in.		Ideal weight 62 kg.	
Observed weight August 13	136.0 kg.		
" " October 19	118.3 "		
Loss in 67 days	17.7 "	127.1 kg.	average weight for period
Daily loss	264 grm.	2.22 sq. m.	= surface area
Of which 80 % as fat	211 "	1920	basal calories for 24 hours
Calories (fat x 9.3)	1962	1997	basal calories for B.M.R. 104 %
Calories from food	1060	999	add 50 % for activities
Total 'weight-loss calories'	3022	2996	'metabolic calories'

Though this method cannot be considered very exact, because of the assumptions discussed above, the close agreement of the figures obtained by two different procedures may be significant. It should be observed, however, that it is possible to obtain similar agreement with other arbitrary values, as can be seen in Table XII.

TABLE XII

Patient J.M. Dietary Period

Calories from food and weight-loss.				Calories from B.M.R.			
Food calories + 100 % weight-loss as fat =	3515			3515 = basal calories + 76 %			
" " 79 % " " " "	= 3000			2996 = " " + 50 %			
" " 60 % " " " "	= 2533			2536 = " " + 27 %			
" " 50 % " " " "	= 2288			2276 = " " + 14 %			
Food calories	= 1060			1997 = basal calories			

Since an exact agreement can be obtained with different proportions of each variable, it becomes a matter of selecting the more probable values. An activity representing more than 50 per cent. over basal metabolism is unlikely for patients living a quiet existence in hospital. It is also improbable that such individuals could live more economically than 27 per cent. over basal. The choice is, therefore, considerably narrowed. The technique illustrated above has been applied to the data for thirty subjects with results showing striking uniformity. Assuming 80 per cent. of fat in the daily loss recorded, the figure so obtained when added to the caloric value of the diet (the weight-loss calories) corresponds to an increase of 44 per cent. over the observed basal calories. A few sluggish individuals showed values as low as 24 per cent. to 30 per cent., while six were over 60 per cent.

If 50 per cent. over the observed basal requirements (the metabolic calorie value) is taken to represent the body needs, the value for fats becomes 86 per cent. for the same cases.

If 15 per cent. to 20 per cent. of the weight lost represents removal of

preformed water from the body, this would only account for 26 to 34 gm., an amount which would hardly be discoverable in the water balance. It should be noticed, however, that there was on the 1,000 calorie diet a slight increase in the average output of urine over that in the higher diets (Table VIII). On the higher initial diets the weight-loss calorie value, taking 80 per cent. of the loss as fat, would represent a somewhat higher increase over the basal metabolism, namely 53 per cent. Since there is a greater water displacement in the initial stages of a subcaloric diet 80 per cent. may be too high, and consequently the other figure may also be reduced. Taking the metabolic figure (basal calories + 50 per cent.) as the fixed point, this would correspond to a fat value of 65 per cent. for the weight-loss during the initial diets.

The periods on thyroid show a similar difference as is illustrated by the records for the same patient mentioned above.

TABLE XIII

J. M. Thyroid Period (14 days at 13.8 grs.)

Observed weight October 19	118.3 kg.		
" " November 2	113.3 "		
Loss in 14 days	5.0 "	115.8 kg. average weight for period	
Daily loss	357 grm.	2.14 sq. m. = surface area	
Of which 80 % as fat	286 "	1850 ideal basal calories for 24 hours	
Calories (fat x 9.3)	2656	2091 basal calories at B.M.R. 113	
Calories from food	1000	1045 add 50 %	
'Weight-loss calories'	3656	3136	'Metabolic calories'

It will be noticed that, although during the thyroid period the average weight of the patient J.M. is much lower, the surface area is only slightly smaller and the theoretical basal metabolism is little different. But as the metabolic rate has now risen by nine points, the body is actually consuming more calories (cf. Table XI). There is really a double increase over the earlier figures for the diet period, since the added 50 per cent. is calculated on the enhanced basal value. Despite this, however, the estimated 3,136 'metabolic calories' fall far short of the figure derived from the weight-loss. The same disagreement was found in all the cases during the thyroid period, the average discrepancy in fifteen cases being 466. It is, therefore, no longer possible to accept *both* the arbitrary figures under discussion, and a new agreement must be sought. Table XIV is drawn up in the same fashion as Table XII.

TABLE XIV

J. M. Thyroid Period

Calories from food and weight-loss.				Calories from observed B.M.R.			
Food calories + 100 % weight-loss as fat	=	4320		3657 = basal calories + 75 %			
" " 80 % " " "	=	3656		3135 = " " + 50 %			
" " 65 % " " "	=	3158		2989 = " " + 43 %			
" " 60 % " " "	=	2992		2654 = " " + 27 %			
" " 50 % " " "	=	2660		2090 = observed basal calories			
Food calories	=	1000		for 24 hours			

It will now be seen that agreement can only be reached by postulating a higher general activity than 50 per cent. over basal or by assuming that a smaller proportion of the weight-loss is due to oxidation of fat. As the increased metabolic rate in most instances is still within the ± 10 per cent. range regarded as normal, an activity of 50 per cent. over basal would still be reasonable in drawing up the 'metabolic value'. It is probable, therefore, that under thyroid the utilization of fat represents a smaller proportion of the weight-loss. Taking the data for the whole series, if 80 per cent. of weight-loss be considered as fat, the increase over the *augmented* basal heat production would require to be 70 per cent.; whereas if the 'metabolic calories' (50 per cent. over basal) be taken as starting-point the fat value of the weight-loss would be only 67 per cent. The increased non-fat portion of the weight-loss under thyroid may be due to removal of extra water from the body or to loss of protein. During thyroid administration there is uniformly an increase in the output of urinary N. But not all the cases show a negative balance, even when allowance of 1 gm. is made for faecal N. It was shown above that the giving of thyroid increased the nitrogen output by 1.6 gm. in eleven cases. This would correspond to about 10 gm. of protein—a relatively small fraction of the total daily loss. In metabolic calculations protein is always regarded as 'flesh', which is considered as being formed by the union of one part of protein with three or four parts of water. The above 10 gm. of protein if taken as 'flesh' would mean a daily loss of 50 gm. or 200 calories, which would explain the whole discrepancy in some of the cases. It may be considered that under administration of thyroid, while the actual loss of weight is greater than on diet only, the character of the loss is different. Fat represents a smaller fraction of the whole, while the proportion of water removed is greater and some of the loss is also due to protein. Cushny (36) states that, when thyroid is given, protein may account for one-sixth of the loss in weight, the remaining five-sixths being due to fat and fluid.

The influence of thyroid extract on the distribution of water in the body is well known, and the drug has been used to get rid of oedematous effusions (37) as well as the myxoedematous deposits of hypothyroidism. The great reduction in the rate of weight-loss which follows withdrawal of thyroid extract (Table IV) may be due to readjustment of the water balance. These observations cover only short periods of time and cannot be taken as suggesting that the extra thyroid loss would be eventually entirely made up when the drug is discontinued. Indeed, this is unlikely, since part of the thyroid loss is due to the raised metabolism—an increased wastage of energy not recoverable. It is possible, too, that some of the protein loss may be due to reduction in size of muscles as the body-weight diminishes. Some patients, after discontinuing thyroid, can maintain their new weight by carefully watching their diet only, but others are unable to do so and require to continue small doses of thyroid indefinitely.

In conclusion, it may be stated that the effect of a subcaloric diet may be

considered in three phases. During the first few days there is a rapid change in weight, due largely to removal of water from the body, possibly the result of readjustment of the glycogen stores. Then follows a period in which about 80 per cent. of the weight-loss is due to disappearance of fat, the balance being due to removal of water; and lastly, there is a tendency for the rate of loss to fall off as the metabolism adjusts itself to the reduced level of food intake. No significant loss of body protein took place on these diets. The greater loss of weight which occurred when the patients were taking thyroid extract while continuing the same diets appears to be of a somewhat different character. No 'dumping' of water was observed during the first few days after the commencement of thyroid, and a habituation to thyroid has not been definitely shown to occur. Under thyroid the loss of weight depends on a different proportion of substances. Fat now accounts only for a little over 60 per cent. of the loss, and there is an increased removal of water from the body. All the patients show an increased utilization of protein, and about half of them have a negative nitrogen balance.

Summary

Reduction in weight has been studied in thirty-five cases of different types of obesity. All the subjects, including marked endocrine cases, lost weight while dieting.

It has been found that the rate of weight-loss bears a definite relation to the caloric value of the diet: the smaller the diet the more the loss.

The rate of loss is greatest at first and decreases as the diet is continued. If the total caloric intake is kept constant at 1,000, the weight-loss is greatest when the carbohydrate of the diet is low.

It has been found that 9 grs. of thyroid extract are required in order to produce a loss of weight equal to that caused by the standard 1,000 calorie diet. The effect of the thyroid is proportionate to the dose given.

The basal metabolic rate for the series of cases was usually within normal range on admission. The rate usually fell during the period of under-nutrition, and was raised about twenty points during the administration of thyroid extract.

The loss of weight when the patients were taking low diets appears to be due to removal of fat and water from the body, but when thyroid is given the utilization of fat represents a smaller fraction of the weight-loss, while the proportion of water removed from the body is greater, and some of the loss may be due to a negative protein balance.

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DIABETIC COMA¹

THE SIGNIFICANCE OF ALTERATION IN THE BLOOD-UREA

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DURING recent years increasing attention has been paid to the blood-urea value in diabetic coma, and particularly to the significance of its increase in prognosis. Cases of diabetic coma presenting retention of urea or non-protein nitrogen in the blood have been noted by a number of observers, but their published findings occur widely distributed through the literature, and the total number of cases is small. Labbé and Boulin (1), who themselves observed five cases and made a full review of the literature, were able to collect only twenty-seven cases of undoubted diabetic coma with nitrogen retention from the contributions of no fewer than seventeen workers. Their study was critical in character, in so far as they rejected any case which did not satisfy their criteria for a diagnosis of diabetic coma, namely excessive hyperglycaemia, reduction of the alkaline reserve of the plasma, and ketonaemia or intense ketonuria. They were justified in taking this attitude, since cases of true uraemia occur with hyperglycaemia accompanying the nitrogen retention. In rare cases the increase in blood-sugar may reach the high levels usually found in diabetic coma.

The material presented here comprises twenty-five cases of diabetic coma in seventeen patients observed during the past five years. We have purposely rejected the records of any case where we knew that the condition was complicated by cardiovascular disease or demonstrable pre-existing renal involvement. We have also eliminated the group of elderly diabetics with so-called hepatic hyperglycaemia. Eleven of the patients are under 40 years of age, and only one over 60 years. Twelve of the cases were known diabetics who had been under treatment in the wards of the Aberdeen Royal Infirmary at various times for a number of years, in some cases from the pre-insulin era. Three patients were in coma twice during the time of this investigation, one patient three times and one patient four times.

In Table I we have shown the blood-sugar and blood-urea values at the commencement of treatment (i.e. I) and after the period of emergency (i.e. II), along with the urinary findings at the onset of coma. The total dosage of insulin during the first twenty-four hours of active therapy

¹ Received January 27, 1932.

is also given. Blood-urea and blood-sugar values were estimated by the methods of Maclean, and blood-chloride by Van Slyke's modification of the Volhard technique.

TABLE I

Case No.	Sex.	Age.	Blood-sugar.		Blood-urea.		Urine.		Insulin Units.	Result.
			1 mg. %.	2 mg. %.	1 mg. %.	2 mg. %.	Sugar.	Ketones.		
1	M	63	518	181	105	44	+++	++	120	R
2	M	45	554	498	214	260	++	+++	200	D
3 A	F	22	562	85	21	—	+	+++	160	R
3 B	F	24	472	97	94	31	+	+++	100	R
3 C	F	25	436	184	120	38	+	++	125	R
4	F	45	412	137	63	—	++	+++	130	R
5 A	F	19	306	271	46	22	++	+++	140	R
5 B	F	20	454	454	33	—	++	+++	130	D
6	M	34	478	197	21	—	+	+++	130	R
7	F	15	478	336	48	49	++	++	80	R
8 A	F	30	522	239	41	—	+	+++	190	R
8 B	F	31	446	181	51	65	+	+++	—	R
9	F	37	512	472	127	156	++	+++	100	D
10	M	23	378	122	46	41	++	+++	100	R
11	M	30	536	236	96	35	++	++	180	R
12	F	39	548	—	146	—	+++	++++	120	D
13	M	46	536	152	59	—	+	+++	180	R
14	F	52	432	386	143	—	++	+++	580	D
15 A	F	21	291	62	36	—	+	++	100	R
15 B	F	21	444	117	31	—	++	+++	90	R
15 C	F	22	75	109	76	11	++	+++	120	R
15 D	F	23	422	58	49	14	++	++	65	R
16	F	50	512	522	80	84	+	++	210	D
17 A	F	17	542	67	—	28	++	+++	110	R
17 B	F	17	512	109	46	—	++	+++	160	R

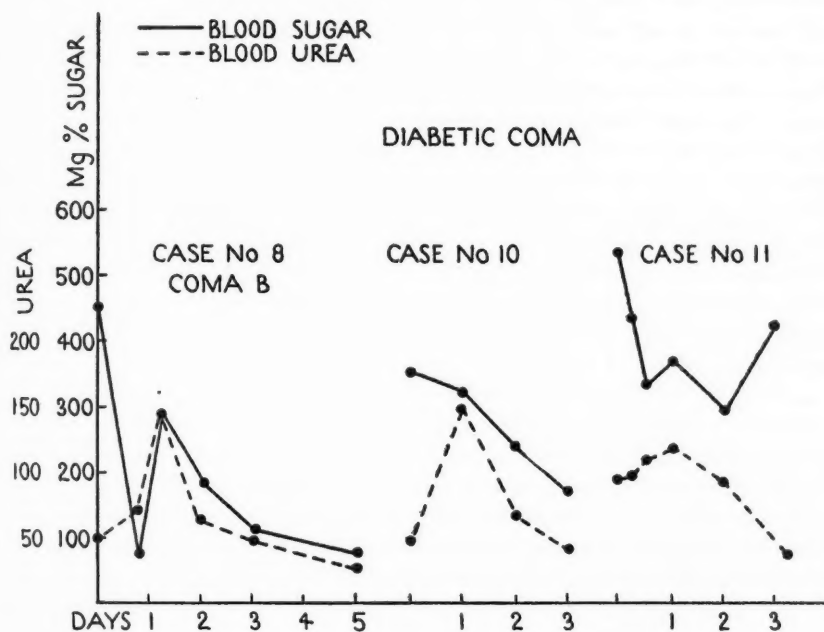
A study of Table I shows that the blood-urea was elevated in nineteen cases. In thirteen this value lay between 40 and 100 mg. per cent., and in six cases was above the latter figure. Where recovery took place the return of the blood-urea to normal was generally rapid. Case No. 3 shows this clearly, as seen in Table II. The patient was observed in three attacks of coma. At the first observation in November 1927, the blood-urea value was normal with an initial blood-sugar value of 562 mg. per cent. In the second attack in October 1929, the blood-urea increased to 94 mg. per cent. and returned to normal within four days. At the third observation in February 1930, the initial blood-urea value was still higher, 120 mg. per cent., and did not return to normal within one month, although six months later the blood-urea value was again normal.

It is important to note that the blood-urea values may show considerable variation during the early stages of active and effective insulin therapy. In three cases actual increase was observed during this period coincident with decrease in the blood-sugar value and marked improvement in the general condition of the patients. In all three cases, however, the blood-urea began to fall within thirty-six hours. The highest values reached were 144, 140, and 116 mg. per cent. in the individual cases (see Graph, p. 355).

TABLE II

Case No. 3.

Second coma period.				Third coma period.		
Date.	Blood-sugar mg. %.	Blood-urea mg. %.	Urine oz.	Date.	Blood-sugar mg. %.	Blood-urea mg. %.
17.10.29	472	94	10	14.2.30	436	120
18	342	73	32	19	408	94
19	81	63	18	21	308	99
21	306	39	38	26	472	76
1.11.29	378	21	74	6.3.30	336	44
				14	412	54
				8.9.30	184	38



Although a moderate degree of nitrogen retention in the blood in the early stages of coma is not necessarily of grave significance, considerable prognostic importance can be placed on retention of any marked degree. In the present series of cases there was only one death where the blood-urea value was normal. In the group of thirteen cases where the blood-urea was increased but did not exceed 100 mg. per cent., one death occurred. In six cases where the blood-urea value was over 100 mg. per cent., there were four deaths. This series of cases is too small for statistical purposes, but, if we take it in conjunction with that collected by Labbé and Boulin, we find a group of fifty-one cases of uncomplicated diabetic coma with elevation of the blood-urea. In twenty-nine of these cases, where the increase in blood-urea was under 100 mg. per cent., there were six deaths, while fourteen out

of twenty-two patients succumbed where the blood-urea value was over 100 mg. per cent.

It is evident from these figures that the estimation of the blood-urea is of great value in the prognosis of cases of diabetic coma. The chances of recovery with suitable treatment are relatively good where the blood-urea is normal or only moderately increased, and correspondingly bad when the blood-urea value exceeds 100 mg. per cent. It would be of importance to know what percentage of cases of diabetic coma exhibit nitrogen retention in any stage of the condition, but it seems difficult to collect a series of cases sufficiently large to illustrate this point. Of our own twenty-five cases, nineteen showed nitrogen retention. Joslin (2) observed fifty-one cases where twenty-four showed nitrogen retention of some degree. It would seem that roughly half the cases of diabetic coma show an elevation of the blood-urea. As is evident from several cases published in the literature, the azotaemia may occur after the period of actual diabetic coma has passed. Merklen, Wolf, and Bicart (3) observed such a case where oliguria and uraemia developed with a fatal issue after the coma had been successfully controlled with insulin. These authors are strongly of the opinion that consideration should be given not only to the degree of glycaemia and ketonaemia in diabetic coma, but also to the blood-urea value, and recommend that the latter should be estimated frequently. With this view we are completely in accord.

Discussion

The cause of the increase in the blood-urea in diabetic coma has not yet been explained. It is evident that the hyperglycaemia itself has no influence on the urea content of the blood, since cases of coma occur without nitrogen retention and, where retention does occur, there is no constant relation between the sugar and urea content of the blood. Brunton (4) studied this question in diabetes and concluded that the concentrations of glucose and urea in the circulation of patients suffering from this disease bore no relation to each other. Insulin therapy itself does not appear to have any effect in raising the blood-urea. Our own cases on insulin had normal blood-urea values outside their periods of coma, and where the blood-urea was moderately increased during coma it returned to normal under effective insulin administration. It should be noted, however, that Joslin (2) considered it possible that large doses of insulin might be a contributory factor in causing nitrogen retention, and quoted the cases published by Bowen and Beck in support of this hypothesis. But a study of the cases seems to show that those requiring most insulin were the cases in which the diabetic coma was most severe in degree and in which nitrogen retention would most probably occur.

The increase in urea, then, is a manifestation of the attack of coma itself, and it is here alone that causative agents must be sought. A reduction in the volume of the blood-plasma with a consequent relative increase in con-

centration of its chemical constituents would bring about a rise in the blood-urea. That this dehydration of the plasma and tissues occurs in most cases of diabetic coma is well established from the clinical side. Polyuria previous to the onset of coma, loss of fluid by vomiting, and lack of fluid intake are all factors concerned in the production of this anhydraemia. Professor J. J. R. Macleod, in a personal communication, has made the interesting suggestion that excessive excretion of water-vapour by hyperpnoea may be an additional factor of some importance. Rowntree, Brown, and Roth (5) have demonstrated the reduction in the plasma volume by direct measurement, while Bulger and Peters (6) pointed to an increase in haemoglobin, a concentration of cells, a moderate rise in non-protein nitrogen, and a slight increase in plasma chlorides and inorganic phosphorus as evidence of dehydration in their cases of diabetic toxæmia. They further showed that a rapid return to normal values of plasma protein took place upon intensive administration of saline and glucose, and that this was accompanied by a remarkable improvement in the excretion of urinary nitrogen and chlorides. Dehydration may, then, be taken to be one factor increasing the blood-urea in diabetic coma just as it is a causative agent in the so-called non-renal uræmias which accompany pyloric stenosis, high intestinal obstruction, post-operative vomiting, peritonitis, pelvic abscess, and diarrhoea. It is, however, a variable factor in different cases of diabetic coma and is certainly not the whole explanation in any individual case, since the constituents of the plasma are not always concentrated to the same relative degree. Thus in case No. 1 of the series of Bulger and Peters (6) the non-protein nitrogen of the blood reached 67 mg. per cent. while the plasma protein did not mount much above normal. In case No. 5, where the plasma protein had increased to 8.59 gm. per cent., the non-protein nitrogen and chlorides were practically normal. It would perhaps be too much to expect complete uniformity in view of the variation that might be present both in the synthesis and excretion of urea and in the excretion of chloride by the kidney and its loss by such incidental factors as vomiting and diarrhoea.

Blum, Grabar, and Van Caulaert (7) made the interesting suggestion from their observations in two cases of diabetic coma that the increase in blood-urea was due neither to nephritis nor to anuria, nor directly to the acidosis itself, but to the depletion of the blood-plasma and tissues of chloride following a prolonged acidosis. In one of their cases the patient was admitted in coma with blood-sugar 355 mg. per cent., alkaline reserve 16, and blood-urea 55. Improvement took place on insulin administration and the blood-urea fell to 45, while the urine still contained albumin and casts. The authors emphasized the fact that there was no retention of urea in the blood at the time when the renal lesion seemed to be at its worst. Upon a chloride-free diet the blood-urea increased to 480 mg. per cent. in six days, while diuresis was good and the urine contained only a trace of albumin and no casts. Upon giving the patient chloride by the mouth the blood-urea returned to normal. A second case showed analogous findings,

but the authors failed to repeat their observations in other cases, and even in one of the same individuals in a later attack of coma. These observations are no doubt of great importance both for prognosis and treatment in patients where hypochloraemia is discovered, and indicate that blood-chloride estimation should be made in cases of diabetic coma, especially if nitrogen retention is present. They are also of significance in supporting the suggestion that urea retention occurs to compensate chloride loss and maintain the osmotic pressure of the blood-plasma in any condition where chloropenia is present. But it is necessary to point out that an examination of the case reports of these patients reveals the fact that both suffered from severe diarrhoea of more than ten days' duration, a complication which would in itself be sufficient to cause marked disturbance of chloride metabolism. Until further evidence is available these cases should be regarded only as isolated instances of a special peculiarity that may occur in diabetic coma. In those cases of our own where the chloride metabolism has been investigated we have found the plasma chloride increased or normal. The investigations made by Bulger and Peters (6) in their cases of diabetic toxæmia revealed blood-chloride values of the same order. In one of our own cases under separate publication (8) the plasma chloride varied between 580 and 627 mg. per cent. during a period of anuria of four days' duration, while the blood-urea value mounted from normal to 230 mg. per cent., the patient meantime receiving adequate intravenous saline with glucose and insulin. The evidence available suggests that in diabetic coma there is retention of both chloride and urea, and it is therefore not possible to regard increase in the blood-urea as secondary to reduction in plasma chloride.

Although diabetic patients, apart from complications, may suffer from the disease for long periods without the occurrence of nitrogen retention in the blood, there is always present nevertheless some degree of disturbance of nitrogen metabolism. In patients with severe diabetes the difficulty found in maintaining a satisfactory nitrogen balance is evidence of this disturbance; the total nitrogen excretion in these cases is greater than the nitrogen content of the protein in the diet. Lyall (9) demonstrated this clearly in patient No. 1 of his series, and showed that even when the protein in the diet was increased to as much as 114 gm. per day, endogenous protein was still being utilized in addition. This excessive catabolism of protein, largely of endogenous origin, is even more marked in the pre-coma stage of diabetes and in coma itself. In consequence increased amounts of urea are thrown into the circulation to be dealt with. It is beside the point for the present argument to consider whether urea is actually formed or whether the ammonia derived from the deamination of amino-acids is directly combined with ketonic acids for excretion. The possibility remains that this excessive break-down of protein tends to increase the urea content of the blood in diabetic coma.

If any degree of renal failure is superadded to these factors already at

work, nitrogen retention proceeds rapidly. There is ample evidence of implication of the kidney in the majority of cases of diabetic coma. In nearly all cases albumin is present in the urine, granular casts and blood are often seen, and oliguria or complete anuria may supervene. Changes in renal secretion may be brought about by any one of, or a combination of, the following interrelated factors: (1) circulatory disturbance in the kidney; (2) osmotic changes in the blood-plasma; (3) actual parenchymal damage due to the toxic action of continued excretion of acids, ketones, sugar, and nitrogenous waste products. Snapper (10) suggested that the kidney is damaged by the prolonged attempt to oxidize ketonic acids. There is no experimental proof of this suggestion, and it seems more probable that the kidney excretes these substances as ammonium salts. Snapper states that the characteristic changes in the kidney at autopsy are glycogen infiltration and coagulative necrosis of the tubule cells, while Armani also described special pathological appearances in the loop of Henle.

Where recovery takes place the renal changes are transitory. In case No. 3 of this series the patient passed through three attacks of coma during three years. The blood-urea was raised during the two later attacks but returned to normal each time and abnormal constituents disappeared from the urine. In the case already mentioned (8) where anuria persisted for four days, the blood-urea eventually returned to normal. The urine after recovery showed no abnormal deposit and the ability to concentrate urea after a test dose was satisfactory.

Summary

1. The importance of alteration in the blood-urea in twenty-five cases of diabetic coma is considered. In cases with a blood-urea over 100 mg. per cent., the mortality is markedly increased.
2. The blood-urea may increase during the early stages of the coma, but begins to fall within thirty-six hours if recovery is to take place.
3. In summing up the evidence available it would seem that dehydration and excessive nitrogen metabolism are minor factors in the production of increase in the blood-urea in diabetic coma, but that when renal involvement supervenes nitrogen retention results as a direct consequence.

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THE QUARTERLY JOURNAL OF MEDICINE

(NEW SERIES)

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THE GASTRIC SECRETION IN PERNICIOUS ANAEMIA¹

BY JOHN F. WILKINSON

(From the Department of Clinical Investigations and Research, the University of Manchester, and Manchester Royal Infirmary)

PART I. *The Secretion of Acid, Chlorides, and Pepsin in Pernicious Anaemia*

THE acidity of normal gastric juice was demonstrated as long ago as 1780 by Spallanzani (110), but the stomach-tube for withdrawing test samples was not employed until later by von Leube (67), Ewald (30), and others. Prior to this, however, the marked changes that had been observed in the gastric mucosa in cases of pernicious anaemia had led Flint (40) to suggest a connexion between the two: 'Nor is it difficult to see how fatal anaemia must follow an amount of degenerative disease reducing the amount of gastric juice so far that the assimilation of food is rendered wholly inadequate to the wants of the body.' This is of singular significance in the light of present-day knowledge. Other observers made similar suggestions (139).

In 1886, Cahn and von Mehrling (13) drew attention to the lack of free hydrochloric acid in the gastric juice of a case of pernicious anaemia, an observation that was confirmed by a large number of observers (30, 32, 62, 76, 125, 138) using meals of the single one-hour sample type.

With the advent of the fractional method of gastric analysis (93) it was possible to evaluate these achlorhydric cases better and to eliminate many with 'apparent' achlorhydria (i.e. achlorhydria at the one-hour interval by the Ewald method). This method further emphasized the profound gastric secretory dysfunction in pernicious anaemia. Many other writers⁽¹⁴⁰⁾ have confirmed the almost invariable occurrence of achlorhydria gastrica in a large number of cases of pernicious anaemia.

That exceptional cases were reported (*vide infra*) having free hydrochloric acid in their gastric secretions did not invalidate this general view, for the rarity of these cases was sufficient to cast grave doubts upon the correctness of the diagnosis of pernicious anaemia.

During recent years there has been much confusion through the indiscriminate use of the term 'achlorhydria' and 'achylia gastrica'. These are not synonymous, although both indicate an absence of free hydrochloric acid from the gastric juice; 'achlorhydria' refers only to an absence of free

¹ Received February 10, 1932.

hydrochloric acid, but in 'achylia gastrica' there is a superadded deficiency of enzyme-like substances acting in an acid or neutral medium although, strictly speaking, it implies cessation of all secretions. Relatively few writers (141) have referred to the enzyme content of human gastric juice—mainly on account of the lack of satisfactory and convenient methods of determination. Nevertheless, it is almost universally agreed that in pernicious anaemia both hydrochloric acid and pepsin are deficient—i.e. achylia gastrica exists. (No account is taken here of the unidentified anti-anaemic principle.) It is a significant fact that this achylia gastrica persists throughout the course of the disease, and is unaffected during remissions and relapses or by treatment; a few cases (see p. 367) have shown a return to normal gastric secretion on recovery. This gastric secretory impairment is present long before the onset of the symptoms of pernicious anaemia, and it is presumptive that the condition is hereditary or familial; the question has already been considered in this *Journal* (133).

In a large series of cases of pernicious anaemia (150 males, 140 females) under observation at the Manchester Royal Infirmary 208 have been examined more than once, in the majority of cases by the method of fractional gastric analysis (8, 93, 94), using the ordinary standard oatmeal gruel test breakfast. All samples obtained (at fifteen-minute intervals) were subjected to routine examinations, (1) qualitatively, for bile, blood, pus, starch, mucus, and lactic acid; (2) quantitatively, for free and total acidities, total and mineral chlorides, and peptic activities.

A. *Results of fractional gastric analyses on 200 cases showing achylia.* For purposes of consideration, the first 200 cases showing achlorhydria gastrica have been taken, certain exceptional cases showing the presence of free hydrochloric acid in the gastric juice being discussed later.

Fasting Contents. Volume. As a rule the fasting contents in pernicious anaemia were of small volume, the average being 15.3 c.c. (maximum 86 c.c.; minimum, nil). The volumes in the 200 cases were distributed as shewn in Table I.

TABLE I

Vol. of Fasting Contents. (c.c.).	No. of Cases.	Per cent.
nil	21	10.5
1-10	76	38.0
11-20	47	23.5
21-30	34	17.0
31-40	14	7.0
41-50	4	2.0
51-86	4	2.0
	<hr/> 200	<hr/> 100.0

It is thus seen that 144 cases, or 72 per cent. of the whole series, had fasting contents less than 21 c.c.; only four exceeded 50 c.c. These volumes are very definitely less than the average volume of 52 c.c. obtained from normal men and women (41, 51, 52) and 51 c.c. from 100 healthy students (8).

Mucus was present, as a rule, in the fasting contents, and very frequently persisted throughout the duration of the test periods. In normal individuals mucus is only present in very small amounts, which vary inversely with the free acidity (5).

Blood was not found in any samples.

Bile was absent in all but thirty cases. It is more commonly found in hyperacidic conditions (5).

Pus was never found on microscopical examination.

Lactic acid was present in two cases. In neither was this confirmed at subsequent tests, and the explanation was found in the fact that both had received lemon and orange fruit juice within a few hours of the test (131). Levine and Ladd (68) found lactic acid in 3 per cent. of their cases, while Stockton (112) also observed it in six cases. It is not found in a normal healthy adult stomach under similar test conditions.

Emptying time of the stomach. This was determined by the absence of (1) starch in the test samples, and (2) sugar in the test-sample filtrates.

The emptying time in this series showed an average of 1.6 hours (maximum, 2.75 hours; minimum, 0.75 hour).

Only five cases showed emptying times of 2.75 hours.

TABLE II

Emptying time (Hours).	No. of Cases.	Per cent.
0-0.75	11	5.5
1.0	28	14.0
1.25-2.0	131	65.5
2.25-2.75	30	15.0
	<hr/> 200	<hr/> 100.0

It will be seen that in 170 (85 per cent.) the stomach was empty at the end of two hours, and 39 (19.5 per cent.) in one hour or less.

The three cases of pernicious anaemia examined by Wills (135) gave an average emptying time of 0.96 hour.

From their series of 100 normal students, Bennett and Ryle found an average of 1.9 hours; and Baird, Campbell, and Hern's series of fifty-seven normal cases averaged 2.1 hours (5). In commenting upon the value of estimating the emptying time of the stomach Rehfuess (94) says: 'We found a remarkable constancy in the rate of emptying, and practically all studies on fractional gastric analysis emphasizes the fact that to-day it is probably the most accurate method of exactly determining the evacuating point of the stomach. . . . The free acid may vary considerably. The evacuation time (of the stomach) usually varies within a relatively small degree.'

Acidities. In the 200 cases which showed a complete absence of free hydrochloric acid in all samples obtained, the total acidities were very low and, as a rule, the titre was approximately 5 to 10 units, occasional samples falling outside these limits, especially in the fasting contents. The higher values were always obtained where bile had been detected. On the whole,

however, the total acidities maintained a relatively constant value of 5 to 10 units.

In the accompanying Chart I the shaded area shows the limits of the total acidities. It will be seen that the great majority of the titres fall below 10 units (cf. Ryle, loc. cit.).

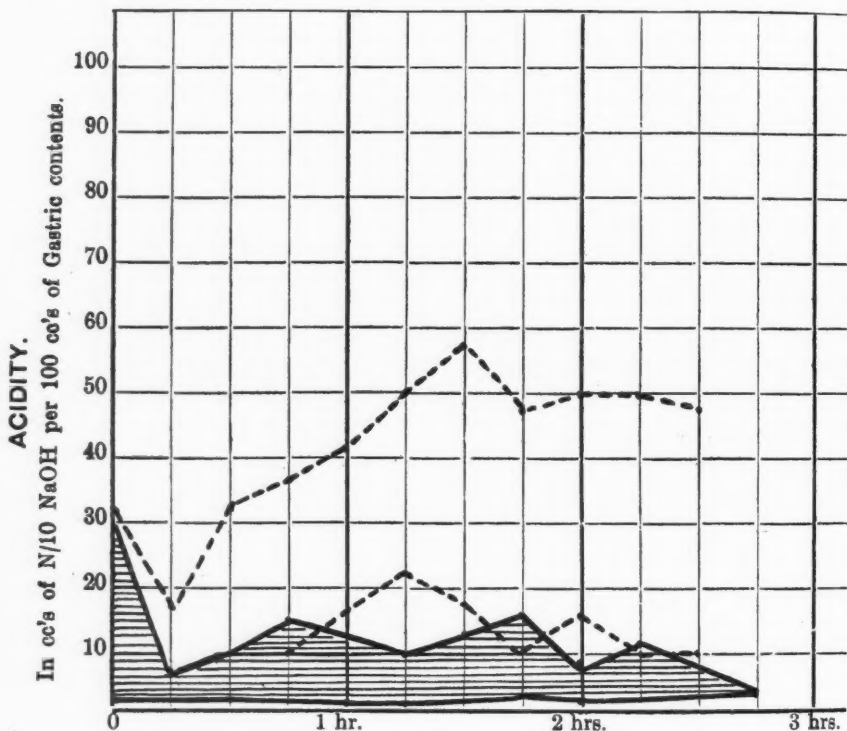


CHART I. Total acidities in 200 cases of pernicious anaemia.

----- Total acidities in 80 per cent. normal individuals (after Ryle, modified).

For purposes of comparison the approximate limits for total acidities in normal individuals are superimposed on Chart I; they have been derived from the standard chart of the limits of free acidities of 80 per cent. of normal people (Bennett and Ryle, loc. cit.) by the arbitrary addition of 10 units—the average difference between free and total acidities.

Total and mineral (inorganic) chlorides. In Chart II the shaded area includes the results obtained in the estimation of total chlorides in the 200 cases of pernicious anaemia. Very few titres fell outside this area (i.e. eleven out of approximately 1,400 separate total chloride titrations), and it thus represents the limits of total chloride secretion in this series. The maximum peak was 95 units (equivalent to 0.372 gm. Cl.). It will be observed also that this area lies almost entirely above the maximum limits for the total acidities. These values are in accordance with those obtained

by Miller and Smith (80) on twenty-two cases of pernicious anaemia, but are below the average for those obtained in individuals with normal secretions (5, 80) (Chart II).

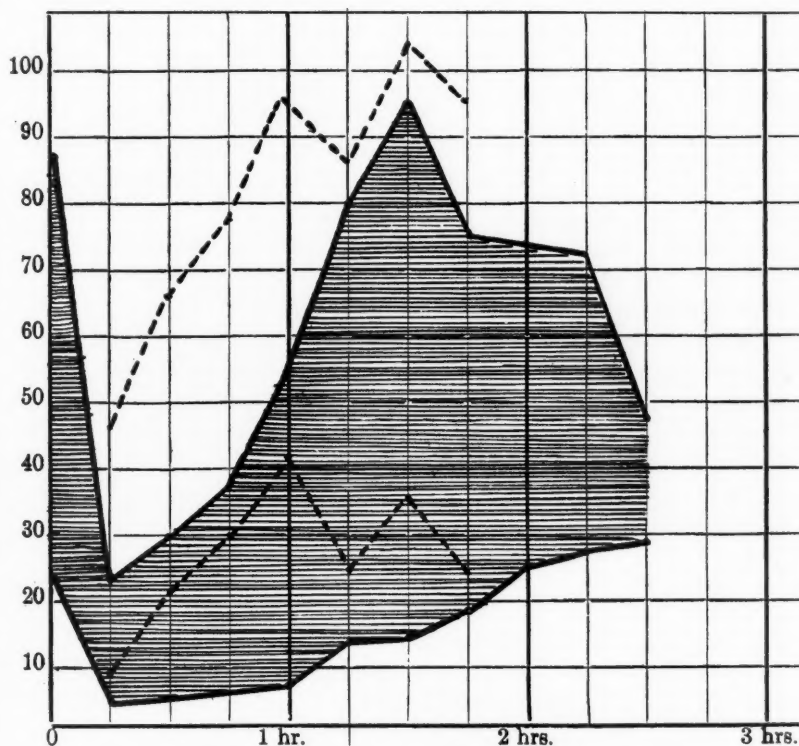


CHART II. Total chloride secretion in 200 cases of pernicious anaemia.

----- Total chloride secretion in normal individuals (after Miller and Smith).

The inorganic chlorides were estimated in 118 cases, and the limits within which these values fall correspond very closely with the total chloride values. In comparing the total and inorganic chloride curves it has been observed that as a rule they run very closely parallel, suggesting that the total chloride titres were almost entirely due to the mineral chloride content of the samples. In contradistinction to the total acidities, it should be noted that considerable variation in the total chloride titres was found in different cases; thus, in one case, a relatively high secretion occurred (Table VII, Case A. B.), while, in another case, a very poor total chloride titre was obtained (Table VII, Case W. S.). Between these all grades of total chloride values were found. The inorganic (mineral) chlorides showed similar variations.

It is not difficult, therefore, to imagine that the chloride secretion (in the absence of duodenal regurgitation) represents far more consistently a truer

picture of the severity of the gastric secretory dysfunction—at least in these cases of pernicious anaemia.

Attempts to correlate these findings with the clinical condition of the patients have failed to disclose any constant relationship, nor has it been possible to associate a more severe anaemia with a low or a high total chloride secretion as opposed to a less severe case.

Peptic activity. Pepsin is readily detected qualitatively in the gastric test samples. On the other hand, peptic ferments can only be estimated quantitatively through their effects, which are profoundly influenced by slight changes in the conditions governing the tests, such as the time, the temperature, and concentration of substrate and enzyme. Thus it is difficult to make these determinations conveniently, with reasonable accuracy and speed. The methods become unwieldy when serial samples from two or three fractional test meals have to be tested daily.

The best available methods depend upon the principle of varying one factor while the others are kept constant. The majority are based upon the digestive power of pepsin on proteins like fibrin, egg-albumen, and edestin; such methods have been described by Mett (78), and modified by Nirenstein and Schiff (81) using egg-albumen in the 'Mett' tubes, and by Reiss (96) and Fischer (38), who employed a refractometric means of determining the peptic digestive capacity.

Fuld and Levison (44) based their 'peptic index' on the lowest dilution of the gastric juice required to digest a known amount of 0.1 per cent. edestin solution in thirty minutes.

Other methods have been described (45, 83, 97, 102, 109), a convenient one being that described in the *United States Pharmacopoeia* (10th ed., 1926, p. 280), using egg-white and determining the enzyme concentration necessary to effect a certain albumen volume in thirty minutes.

According to Bayliss (7): 'When comparing the action of different strengths of enzyme solution, it is advisable to take as the basis of comparison the times taken to effect equal change, rather than the amounts of change in equal times.'

For serial pepsin determination it was necessary to use some method that was conveniently rapid, simple, and moderately accurate; the following has served as a useful measure of peptic activity. A 0.1 per cent. solution of edestin in 0.12 per cent. hydrochloric acid is made up and keeps well in a refrigerator until required. The filtered gastric juice (2 vols.), edestin solution (25 vols.), and distilled water (3 vols.) are quickly mixed, shaken, and incubated at 37° C. At frequent intervals samples are withdrawn with a small pipette and run into 1 c.c. of saturated brine—an immediate opalescence indicating incomplete digestion; further tests are made and the time noted for complete digestion when the brine remains clear after addition of the sample. Experience has shown that a rough preliminary guide of the time can be obtained from the acidity titres, although there is actually no constant relationship; when normal acidity or hyperacidity are

present frequent test samples will be necessary after ten minutes. Using this method, normal gastric juice gives values of twelve to eighteen minutes.

The results obtained represent the time required for 100 c.c. of the gastric juice to digest 1,250 mgm. of edestin. In nearly every case in this group the peptic activities of all samples were reduced to negligible limits as compared to the values obtained for normal gastric juice using this method. Other workers (68) have observed similar results, although some (88) consider that small quantities of pepsin are still secreted.

The results obtained in this series of 200 cases of pernicious anaemia are conveniently summarized in Table III.

TABLE III

Gastric Secretion in 200 Cases of Pernicious Anaemia showing Achylia

	This Series.	Normal.
Emptying time (average)	1.6 hours	2 hours (Bennett and Ryle)
Fasting contents (average)	15.3 c.c.	52-4 c.c. (Bennett and Ryle, Rehfuess)
Mucus	+ +	Traces
Blood	Nil	Nil
Bile (average)	15 per cent.	40 per cent., variable (Ryle)
Pus	Nil	Nil
Lactic acid (thiophene test)	2 doubtful cases	Nil
Free hydrochloric acid (fasting contents)	Nil	0-60 (Bennett and Ryle)
Total acidity (fasting contents)	2-28 units	
Total chlorides (fasting contents)	22-88 units	
Inorganic chlorides (fasting contents) (118 cases)	2-85 units	
Peptic activity (digestion time)	Nil	12-18 minutes

B. *Occurrence of free hydrochloric acid in pernicious anaemia.* The almost invariable occurrence of achlorhydria gastrica in pernicious anaemia has been repeatedly stressed by many writers (142) who considered that it was present in 100 per cent. of a very large series of cases, the presence of free hydrochloric acid suggesting an error in the diagnosis. From time to time, however, occasional undoubted cases of pernicious anaemia have been reported having normal or diminished amounts of hydrochloric acid in their gastric secretions, whilst a few others have been less adequately reported. These are shown in Tables IV and V.

Bloch (10) suggested that the free hydrochloric acid was secreted again during the remissions in the condition, and it is interesting to note that Shaw (106), Seyderhelm and Opitz (104), Connery and Jolliffe (21), McPeak and Neighbors (74), Hurst (1930, 1932) have all observed this return of free acid in the gastric secretion; Campbell and Conybeare (14) and Löwenberg and Gottheil (71) have also found free hydrochloric acid in two cases several years after they first came under observation, but test meals were not done before the commencement of treatment (Table V).

Davidson (25) described a case of pernicious anaemia associated with free hydrochloric acid and duodenal ulcer. The remarkably large number of cases, 15 out of 57, observed by Friedenwald and Morrison (43) were not described, no blood counts being included; of these, 11 showed hypo-acidity (5-12 units) and 4 normal acidities (32-44 units). There does not appear to be any evidence for a diagnosis of pernicious anaemia in the published notes of two of Grinker's cases (49).

TABLE IV

Cases of Pernicious Anaemia with Free Hydrochloric Acid before Treatment

Observer.	Reference.	No. of Cases.	Remarks.
Bloch	10	1	Evidence inadequate
Cabot	12	1	No blood counts given
Carr	16	3	No blood counts given
Davidson	25	1	Associated with duodenal ulcer
Einhorn	29	1	No blood counts given
Faber, Bloch	32	1	
Faber, Gram	33	4	One had syphilis
Falconer, Morris	36	1	'Practically no free HCl,' 'ferments present'
French	42	2	One 'abundant' the other 'deficient' HCl.
Friedenwald, Morrison	43	15	No blood counts given
Grinker	49	3	Evidence inadequate in two
Heath	53	2	
Herzberg, Hürter	56, 61	1	Leukocytosis, myeloblasts, myelocytes
Levine, Ladd	68	3	
Munford	80 A	2	One showed decreasing HCl, ultimately achlorhydria
Panton, Maitland-Jones, Riddoch	85	2	No blood counts given
Passey	86	1	
Percy	87	1	No blood counts given
Reckzeh	92	1	
Reicher	95	1	
Schmidt	101	2	No blood counts given
Shackle	105	1	
Stern	111	1	
Stockton	112	3	No blood counts given
Strauss	113	2	No blood counts given
Strieck	114	2	No blood counts given
Talma	116	1	No blood counts given
Taubman	117	1	
Ungley	119	3	
Weber	124	2	
Willebrand	129	1	

The much-criticized case of Herzberg's (56) showed unusually high leucocyte counts—ultimately reaching 70,000 with the presence of myeloblasts and myelocytes.

Levine and Ladd (68) doubted the diagnosis of two of their three cases.

Of the two cases described by Munford (80 A) one showed a diminishing free acidity over a period of twelve months to an ultimate achlorhydria; the other had a maximum free hydrochloric acid titre of 41 units in the

fifth sample. Both cases lacked many of the characteristic clinical features of pernicious anaemia.

The diagnoses in the two cases of Reckzeh (92) and Stern (111) appear to have been in doubt, carcinoma of the stomach not having been ruled out.

Ungley (119) observed four cases out of seventy-three showing free hydrochloric acid, the first being one of pernicious anaemia of pregnancy, the second atypical, but the other two appeared to be true cases of pernicious anaemia.

TABLE V

Cases of Pernicious Anaemia with Free Hydrochloric Acid returned after Treatment

	Reference.	Cases.	Free HCl. present.
Campbell, Conybeare	14	1	7 years later; not examined before treatment
Connery, Jolliffe	21	1	After a few weeks of treatment
Hurst	59	3	
Loewenberg, Gottheil	71	1	After liver therapy; not examined before treatment
McPeak, Neighbors	74	1	After 4 months' liver treatment
Seyderhelm, Opitz	104	1	After 3 weeks' liver treatment
Shaw	106	1	2 years later

Hurst (1925) also reported two cases that were thought to have been pernicious anaemia until free hydrochloric acid was found in the gastric secretion; further investigations, however, showed them to be cases of Hodgkin's disease and infective endocarditis respectively.

Barnes (6) and Macbride and Carmichael (73) also collected nine and fourteen cases respectively of subacute combined degeneration of the spinal cord showing free hydrochloric acid in the gastric secretion, contrary to the usual achylia gastrica (60, 120).

It is interesting to note that cases with megalocytic anaemia and free hydrochloric acid in the gastric juice, following gastro-intestinal fistulae (17, 35, 70, 79) have been described.

The case described by Heeres (54) was really one of pernicious anaemia of pregnancy (cf. 130).

During the examination of the series of cases of pernicious anaemia (*vide supra*) some eight other cases came under suspicion regarding the correctness of their diagnoses owing to the presence of free hydrochloric acid in their gastric secretions. These cases have been subjected to closer investigations.

Case I. A married woman, aged 39 years, admitted to the Manchester Royal Infirmary suffering from a severe degree of anaemia, weakness, loss of appetite, and slight flatulence, had been quite well until April, 1929, when she became pregnant for the second time; she commenced with sickness, pallor, and weakness of increasing severity, but there was never any history of diarrhoea, sore tongue, or indigestion.

In November of the same year, her condition was much worse and she began to have considerable oedema of the legs and feet. In the following

month a therapeutic abortion was induced and she was subsequently admitted to the Manchester Royal Infirmary on account of her profound anaemia.

There was neither a family history of pernicious anaemia nor a suggestion of familial achlorhydria (cf. 133), her one child was well. Previous medical history disclosed rheumatic and scarlet fevers only.

Examination showed a marked lemon-yellow colour of the skin, slight wasting, artificial teeth, no glossitis or oral sepsis. The liver and spleen were not palpable and there was nothing else abnormal to be found. Reflexes normal.

Blood count: red blood-cells, 1,290,000; white blood-cells, 2,700; haemoglobin, 28 per cent.; colour index, 1.12; polymorphonuclears, 67.5; lymphocytes, 23.0; large mononuclears, 4.0; eosinophils, 5.5; basophils, 0.0; platelets diminished; aniso- and poikilocytosis marked; nucleated red cells present.

Fractional gastric analysis showed the presence of free hydrochloric acid—0 (fasting contents), 0, 4, 11, 18, 11, 7, 0, units respectively in successive 15-minute samples.

She was given one ounce by weight of desiccated hog's stomach daily and was discharged from hospital five weeks later with a blood count of: red blood-cells, 3,704,000; white blood-cells, 4,200; haemoglobin, 60 per cent.; colour index, 0.8; abundant platelets; slight aniso- and poikilocytosis; no nucleated red-cells.

She continued to take one ounce of the desiccated stomach daily for four weeks only and then discontinued it. When seen twelve months later, she had remained perfectly well without any symptoms of the anaemia, and the blood count was: red blood-cells, 4,900,000; white blood-cells, 4,400; haemoglobin, 90 per cent.; colour index, 0.9; abundant platelets and slight anisocytosis only.

Case II. A multiparae, aged 30 years, was admitted complaining of anaemia, dyspnoea, palpitation, and oedema of the ankles, which had got progressively worse after a premature (six weeks) confinement three months previously. There was no complaint of sore tongue, diarrhoea, indigestion, or paraesthesiae. She had had a mastoid operation sixteen years previously but the left ear had discharged frequently since then. There had been four normal pregnancies (one child died at six months, one was healthy and the other two had rickets and tuberculous peritonitis respectively) without subsequent complications. There was no family history of pernicious anaemia or possible achlorhydria.

Examination: considerable pallor of a yellowish colour; furred tongue, pyorrhoea, and oedema of the lower limbs; weight 6st. 9 lb.; the pupils and discs were normal. There was evidence of bronchitis; the liver and spleen were just palpable; reflexes were present and normal. There was a haemic systolic bruit at the apex of the heart; blood-pressure 105/60. The Wassermann reaction was negative. Fractional gastric analysis showed a normal hydrochloric acid secretion—14 (fasting contents), 9, 15, 25, 31, 41, 39, 39, 34, 24 units respectively in successive 15-minute samples.

Blood count: red blood-cells, 600,000; white blood-cells, 4,600; haemoglobin, 18 per cent.; colour index, 1.5; polymorphonuclears, 37.25; lymphocytes, 56.25; large mononuclears, 0.5; eosinophils, 6.0; basophils, 0.0; platelets scanty; marked aniso- and poikilocytosis, nucleated red cells, polychromasia and punctate basophilia present.

She was treated with fresh liver (8 oz. daily) and responded rapidly. After discharge from hospital she was not seen again for twenty months when her blood count was red blood-cells, 4,300,000; white blood-cells, 5,000; haemoglobin 86 per cent.; colour index, 0.9; normal differential white count, abundant platelets, slight anisocytosis. Fractional gastric analysis still showed normal secretions. She had not had any treatment and did not complain of any return of anaemia, although she had had a full-time normal pregnancy four months previously. After a further five months the blood count showed red blood-cells, 5,225,000; white blood-cells, 6,250; haemoglobin, 95 per cent.; colour index, 0.92. She did not attend again until twelve months later, when a similar history of another full-term pregnancy eight weeks previously was given without any return of anaemia; no treatment had been followed.

The blood count was red blood-cells, 5,000,000; white blood-cells, 2,600; haemoglobin, 82 per cent.; colour index, 0.82; platelets abundant; some anisocytosis; no abnormal cells or staining.

In each of these cases it will be noted that the severe anaemia was directly due to the pregnancy (dating from commencement of pregnancy and puerperium respectively) and the blood counts were of the typical primary (pernicious) type. On the other hand, the gastric secretions were normal—a condition of extreme rarity in true pernicious anaemia. In both cases previous pregnancies had not produced anaemia, while in the second case two subsequent ones had failed to cause recurrences. Both cases are apparently cured completely with normal blood pictures and have not had treatment for two and four years respectively in each case. These are definite cases of pernicious anaemia of pregnancy.

Case III. A carter, aged 34 years, was well until September 13, 1930, when he had to cease work owing to weakness, nausea, severe headaches, pain in the back, and cramp in the legs. For a few weeks prior to this date he had noticed the onset of a progressive pallor of the skin, and mucous membranes with a feeling of weakness in the legs, slight sore tongue, and profuse perspiration; there was no history of diarrhoea, indigestion, or loss of weight. He had had pneumonia twice (1902), and bronchitis all his life. There was no relevant family history.

Examination: skin and mucous membranes had a lemon-yellow colour; edentulous; tongue showed early glossitis; weight 8 st. 4 lb.; spleen slightly enlarged; reflexes present. Blood Wassermann reaction negative.

Blood count: red blood-cells, 1,100,000; white blood-cells, 5,600; haemoglobin, 30 per cent.; colour index, 1.36; polymorphonuclears, 69.75; lymphocytes, 21.75; large mononuclears, 5.75; eosinophils, 0.75; basophils, 0.75; basophil myelocytes, 0.75; neutrophil myelocytes, 0.5; 5 normoblasts and 14 megaloblasts per 400 white blood-cells; polychromasia and punctate basophilia marked; platelets diminished; marked anisocytosis and poikilocytosis.

Blood coagulation time 2 min. 20 sec. at 37° C.; bleeding time 1 min. 10 sec. X-ray examinations of chest and gastro-intestinal tract negative. Van den Bergh reaction—positive indirect.

Fractional gastric analysis showed free hydrochloric acid present in all samples—30 (fasting contents), 11, 23, 34, 36, 41, 50, 52, 38, 39, 47 units respectively in successive 15-minute samples.

The patient was given 30 grm. of desiccated hog's stomach daily and showed a rapid response clinically and haematologically (see Table VI). On the 31st day of treatment iron and ammonium citrate (3.9 grm. daily) was added to this therapy. The patient made an uninterrupted recovery and was discharged on the 56th day to continue the desiccated stomach therapy (30 grm. daily). As will be seen from the table his blood showed a rapid return to a normal blood picture and there was an entire freedom from the signs and symptoms of anaemia; he returned to and has continued his full-time work up to the present time.

Clinically, this case is one of typical pernicious anaemia and is supported by the repeated blood examinations. On the other hand, the gastric analysis showed a normal acidity. The satisfactory response to treatment with hog's stomach is also to be noted, and it is believed that this case is one of true pernicious anaemia.

TABLE VI

Day.	Red Blood Cells.	White Blood Cells.	Percentage Haemoglobin.	Colour Index.
1	1,100,000	5,600	30	1.36
10	1,672,000	5,600	36	1.09
23	2,420,000	9,500	38	0.8
31	2,072,000	7,300	36	0.89
42	2,352,000	4,900	44	0.96
56	2,740,000	3,800	52	0.94
88	2,900,000	7,600	56	0.97
104	3,600,000	6,900	72	1.0
132	4,200,000	6,300	80	0.95
160	4,400,000	6,600	84	0.95
174	4,750,000	5,800	88	0.9
188	4,980,000	8,100	88	0.9
244	4,920,000	6,300	94	0.95
328	5,020,000	5,900	94	0.94
356	4,610,000	6,100	100	1.08
422	4,900,000	7,800	94	0.98

Case IV. A printer's assistant, female, aged 46 years, complained of weakness and pain in the upper part of the chest, associated with a 'choking sensation'. Five years previously she had gone very pale and this was followed by swelling of the legs and shortness of breath on exertion. She improved under treatment and was well until seven months prior to admission to hospital when she had a slight attack of jaundice, she improved but never gained her former strength. There was a history of indigestion for about three years and loss of weight recently, but no diarrhoea, sore tongue, or paraesthesiae. Her appetite was good; she had had parotitis six years previously.

Her father had been troubled with recurrent diarrhoea, but died aged 65 years of a 'stroke', her mother also died aged 81 years, and had been troubled with indigestion; her brothers and sisters were well.

Examination: a fairly well-nourished woman, weight 7 st. 6 lb.; edentulous. Tongue clean and moist; spleen enlarged, right kidney palpable; reflexes normal; urine contained a trace of albumin, nothing else of importance noted. X-ray examination of chest and alimentary tract negative. Blood Wassermann reaction—negative.

Blood coagulated in 1 min. 30 sec. at 37° C.; haemolysis began in 0.40 per cent. and was complete in 0.32 per cent. saline.

Blood count on 7.4.30: red blood-cells, 5,790,000; white blood-cells, 5,900; haemoglobin, 78 per cent.; colour index, 0.66; polymorphonuclears, 63.75; lymphocytes, 30.5; large mononuclears, 3.5; eosinophils, 2.25; basophils, nil; platelets fairly abundant; slight anisocytosis and poikilocytosis; no abnormal staining.

Fractional gastric analysis showed a complete absence of free hydrochloric acid and pepsin. The test was repeated after histamine (0.25 mg.) and free hydrochloric acid (4 units) was found in the fourth sample (after one hour). On 22.4.30, red blood-cells, 4,210,000; white blood-cells, 4,800; haemoglobin, 84 per cent.; colour index, 1.0; slight aniso- and poikilocytosis.

There was nothing to suggest pernicious anaemia in the blood picture, but the presence of achlorhydria gastrica was significant despite the low colour index. At this period observations had disclosed the frequent occurrence of a low colour index (also observed by other workers), (a) during the course of treatment of some cases of pernicious anaemia, and (b) in the early histories of cases that had been attending the Out-patient Department of the Manchester Royal Infirmary and later developed frank pernicious anaemia.

For this reason, the patient was given a mixture of hydrochloric acid and pepsin (132) and examined at regular intervals. On 26.6.30, the blood count was: red blood-cells, 3,200,000; white blood-cells, 5,300; haemoglobin, 90 per cent.; colour index, 1.4; platelets moderate; anisocytosis and poikilocytosis marked. The case was now obviously one of pernicious anaemia and she was given a desiccated hog's stomach preparation (25 gm. daily) to which she responded very well indeed (127) showing a return to normal blood picture. This case clearly demonstrates the value of a gastric analysis in the early stages before the blood picture has developed its characteristic features.

Case V. A Jewess, aged 55 years, was admitted to hospital complaining of vague abdominal pains, flatulence, dizziness, persistent headaches, weakness, attacks of vomiting and constipation, with increasing severity during the previous twelve months. There was also numbness of the legs, paraesthesiae in the fingers and sore gums but no diarrhoea or sore tongue. One son had had jaundice; nothing else relevant in the family or previous medical histories.

Examination: patient had a yellowish colour but the sclerotics were clear; tongue, pale and smooth; pyorrhoea marked; reflexes present; spleen and liver not enlarged; nothing else abnormal. The urine did not contain albumin, casts, or sugar; the faeces did not furnish any evidence of helminthiasis. Blood urea: 27 mg. per 100 c.c.

12.6.28. Blood count: red cells, 4,000,000; haemoglobin, 90 per cent.; white cells, 3,100; colour index, 1.1; eosinophils, 5.0 per cent.; platelets scanty; aniso- and poikilocytosis present. Fractional gastric analysis showed achlorhydria.

5.3.29. Red cell count, 3,400,000; haemoglobin, 78 per cent.; white cells, 4,500; colour index, 1.15; eosinophils, 4.5 per cent.; platelets scanty; anisocytosis and poikilocytosis present. Fractional gastric analysis showed free hydrochloric acid of 5 and 2 units in the samples obtained at three-quarters and one hour respectively.

12.6.29. Patient much improved on hydrochloric acid and pepsin mixture. Taking liver, $\frac{1}{4}$ lb. per day. Blood count: red blood-cells, 5,025,000;

haemoglobin, 92 per cent.; white blood-cells, 3,100; colour index, 0.92; eosinophils, 1.2 per cent.; slight aniso- and poikilocytosis.

18.11.29. Still taking fresh liver ($\frac{1}{4}$ lb. per day) and hydrochloric acid mixture. Indigestion still present, also paraesthesiae. Red cell count, 4,710,000; haemoglobin, 100 per cent.; colour index, 1.06; white blood-cells, 4,700; eosinophils, 1.2 per cent. Fractional gastric analysis showed free hydrochloric, 3, 2, and 2 units at samples 0, $1\frac{1}{2}$, and $1\frac{3}{4}$ hours respectively.

28.5.30. Has been taking raw liver daily and occasional liver extract. Still has paraesthesiae of hands and feet. Red cell count, 4,500,000; haemoglobin, 96 per cent.; white blood-cells, 6,400; colour index, 1.1; eosinophils, 24.25 per cent.; slight anisocytosis and poikilocytosis.

10.6.31. Red cell count, 4,800,000; haemoglobin, 98 per cent.; white blood-cells, 4,300; colour index, 1.1; eosinophils, 18.5 per cent.

4.1.32. Red cell count, 4,980,000; haemoglobin, 92 per cent.; white blood-cells, 6,700; colour index, 0.92; eosinophils, 10.0 per cent.

It is noteworthy that in this case a very marked eosinophilia was observed after the patient began to take the liver diet raw instead of well cooked. The eosinophils had never exceeded 5.5 per cent. until 20.3.30 when they suddenly increased to 11.0 per cent. and then 15.5 per cent. four weeks later. From that time onwards until 18.11.31, the eosinophil count (taken at monthly intervals) was between 15.5 per cent. and 24.25 per cent.; on 4.1.32, it was 10 per cent. with the exception of that on 5.3.29, the other blood counts were never really typical for pernicious anaemia, but this can be readily understood since large quantities of fresh liver and liver extract were administered following the typical count on 5.3.29. The free acid found on two occasions was of very low titre and it seems reasonable to consider this as a possible case of pernicious anaemia.

Case VI. A shunter, aged 59 years, when seen in the Out-patient Department of the Manchester Royal Infirmary (June 1928), complained of pains in the back and legs (of three months' duration), together with numbness of the feet. He had been off work for twelve weeks on account of an attack of bronchitis. He was seen by me for the first time on March 24, 1930, and was suffering from pains in the back, flatulent dyspepsia, sore tongue, and pins and needles, numbness and cramp in the legs. He had just recovered from another attack of bronchitis.

Examination showed considerable pyorrhoea; some glossitis; no enlarged spleen or liver. Knee- and ankle-jerk reflexes very sluggish. Nothing else abnormal found. Blood count showed:—red blood-cells, 4,000,000; white blood-cells, 7,800; haemoglobin, 104 per cent.; colour index, 1.3; anisocytosis present; platelets abundant; no abnormal staining. Wassermann reaction was negative. Fractional gastric analysis showed a free acidity of 2, 1, and 7 units in samples at 1, $1\frac{1}{4}$, and $1\frac{1}{2}$ hours respectively.

It was considered that this might be a case showing the early pernicious anaemia-subacute-combined-degeneration of the spinal cord syndrome, and the patient was treated with desiccated hog's stomach (30 grm. daily) and a mixture containing pepsin and hydrochloric acid. He showed a rapid response, and was quite well on May 12, 1930, with a blood count of red blood-cells, 5,016,000; white blood-cells, 8,100; haemoglobin, 90 per cent.; colour index, 0.9; platelets abundant; no anisocytosis or other abnormal features. The dose of hog's stomach was reduced to half.

He was not seen again until November 5, 1930, when he gave the following history: In June (1930) he had had his bad teeth removed, and since that date had been troubled with frequent attacks of sore throat and dysphagia. He had discontinued hog's-stomach treatment for about two months. For several weeks he had pain in the right side of the mouth and ear, dysphagia was much worse, but he had not lost weight.

Examination showed some small hard glands on the right side of the neck below the angle of the jaw, and an epitheliomatous ulcer on the soft palate and right fauces. Treatment with radium emanation (sixteen tubes inserted for six days, followed two weeks later by nine tubes for five days) was given at the Manchester Radium Institute by the late Dr. Birkett. Four weeks later his blood count was:—red blood-cells, 4,312,000; white blood-cells, 10,800; haemoglobin, 90 per cent.; colour index, 1.04; polymorphonuclears, 69.0; lymphocytes, 25.75; large mononuclears, 1.0; eosinophils, 3.75; basophils, 0.5; platelets abundant and slight anisocytosis.

In this case, however, while the evidence was weakened by the presence of small amounts of hydrochloric acid in the gastric secretion the clinical features and blood pictures were fully in keeping with a diagnosis of early pernicious anaemia with subacute combined degeneration of the spinal cord at least four months before any symptoms or signs of malignancy had become manifest. It should be noted also that two years previously the patient had complained of the symptoms frequently associated with postero-lateral involvement of the cord, and these could hardly be ascribed to the later malignant condition.

One must not overlook the fact that occasionally cases of malignant disease may have blood pictures somewhat resembling pernicious anaemia, but they do not respond to the liver treatment. In Case VI there was a definite response to the hog's-stomach therapy. Viewing the facts as a whole, therefore, one is inclined to consider that this case was originally one of pernicious anaemia, the malignant condition supervening later.

Case VII. A housewife, aged 34, complained of anaemia, which became marked following a hysterectomy for endometrioma two years previously. She was always tired, short of breath, and complained of palpitation, flatulent dyspepsia, increasing yellowish pallor, paraesthesiae of fingers, and rheumatic pains in limbs. Her appetite was good, the bowels were regular, and there had not been any diarrhoea or sore tongue. The feet used to swell before her operation, but only occasionally since. In October 1929 she became very jaundiced, but this had improved again for a time. She had a relapse and was put on to liver diet, which made her very sick, causing considerable indigestion. She gradually became worse, and was admitted to hospital on July 17, 1930.

Examination: Extreme yellowish pallor of skin and mucous membranes; upper dentures, lower teeth good; tongue slightly furred; weight, 7 st. 2 lb.; spleen enlarged $1\frac{1}{2}$ in. below costal margin but not tender; liver not enlarged; reflexes present; occasional extrasystoles. Wassermann reaction, negative. Van den Bergh reaction, positive delayed. X-ray examination of alimentary tract, negative.

Fractional gastric analyses showed normal hydrochloric acid secretions on several occasions, thus (21.7.30) 0, 0, 3, 4, 12, 17, 15, 15, 9, 4, 5 units, and on 10.9.30 (after receiving histamine daily for two weeks, subcutaneously), 9, 2, 5, 12, 15, 22, 26, 18, 19, 17 units.

Blood count (17.7.31): red cell, 1,470,000; white cell count, 3,700; haemoglobin, 37 per cent; colour index, 1.3; marked aniso- and poikilocytosis; occasional normoblasts and megaloblasts.

She was given daily injections of histamine for two weeks, the clear gastric juice aspirated, incubated with beef muscle according to the method described by Castle (17) and administered daily to another case of pernicious anaemia, which failed to respond to this treatment (17, 127), thus demonstrating the absence of the 'anti-pernicious anaemia' principle from the gastric juice. At the end of two weeks this patient was treated with desiccated stomach (30 grm. daily) with a rapid recovery, and was discharged with a count of red cells, 4,000,000; haemoglobin, 78 per cent.; colour index, 0.9. She continued to improve, and on 10.9.30 showed a count of red cells, 4,750,000; haemoglobin, 72 per cent. She was not seen again for three months, when she developed a cystitis—the stomach treatment having also been discontinued. The blood count (13.1.31) showed red blood-cells, 2,570,000; haemoglobin, 44 per cent.; white cells, 4,900; colour index, 0.86; slight aniso- and poikilocytosis; a few normoblasts and megaloblasts; platelets abundant.

The cystitis was treated vigorously and the stomach therapy reinstituted with a marked improvement in the condition for four months, when she contracted influenza again. She remained at home, and when next seen had relapsed somewhat.

On 10.7.31 the blood count was red cells, 1,610,000; haemoglobin, 32 per cent.; white cells, 3,500; colour index, 1.0; aniso- and poikilocytosis; normoblasts and megaloblasts present. The patient declined readmission to hospital, so intramuscular therapy with a liver preparation (128) was instituted for seven days with again an improvement in the blood condition to red cells, 2,750,000; haemoglobin, 54 per cent.; colour index, 1.0; aniso- and poikilocytosis; platelets scanty; no normoblasts or megaloblasts. She then discontinued her attendances.

There does not appear to be any doubt that this case was one of pernicious anaemia; the large number of blood counts were typical, showing megaloblasts, megalocytes, normoblasts, usually a high colour index, and scanty platelets. Although the gastric juice contained free hydrochloric acid, it was deficient in the 'anti-pernicious anaemia principle'. This case also illustrates the profound effects on the blood picture of sepsis and infections such as cystitis and influenza.

Case VIII. A labourer, aged 34, was admitted to hospital complaining of progressive weakness of six months' duration, associated with palpitations, shortness of breath, headaches, vague abdominal pains and flatulence, increasing yellowness of the skin, and paraesthesiae in both hands; there was some looseness of the bowels, but no sore tongue or marked loss of weight. There was nothing relevant in the family and previous medical histories.

Examination: Tongue clean and moist, but slight papillary atrophy; very marked pyorrhoea; skin showed a yellow colour, with brownish pigmentation of the forearms; weight, 8 st. 13 lb.; liver and spleen not enlarged; reflexes present; nothing else found on examination. X-ray examination of chest and alimentary tract, negative. Wassermann reaction, negative. Van den Bergh reaction, negative.

Blood count (19.7.30): Red cell count, 2,400,000; haemoglobin, 52 per cent.; white cell count, 3,800; colour index, 1.1; aniso- and poikilocytosis

very marked; occasional megaloblasts; platelets present. Fractional gastric analysis showed free hydrochloric acid, 8 units present at the one-hour sample.

He was given 30 grm. daily of desiccated stomach powder (127), and on 19.8.30 left hospital at his own request with a blood count of 3,800,000; haemoglobin, 76 per cent.; colour index, 1.0. He did not continue adequate treatment (less than 6 grm. daily), and was readmitted to hospital. The blood count (6.7.31) was red cells, 1,400,000; haemoglobin, 42 per cent.; colour index, 1.5; platelets scanty; very marked aniso- and poikilocytosis; megaloblasts, normoblasts, and punctate basophilia present. His condition was complicated by an acute follicular tonsillitis, and the blood count fell to (27.7.31) red cells, 1,290,000; haemoglobin, 41 per cent.; colour index, 1.58.

He was given hog's stomach (30 grm. daily), and later this was supplemented by eight intramuscular injections of 5 c.c. of Hepatex P.A.F. (128). The blood count increased very slowly to (10.9.31) red cells, 3,300,000; haemoglobin, 72 per cent.; colour index, 1.09; when he was discharged at his own request.

In the period of eighteen months during which this patient was under observation all the thirty-seven blood counts were typical for pernicious anaemia, but at no time was a high reticulocyte count obtained, the maximum being 13.8 per cent. after the continued hog's stomach-parenteral liver therapy.

The presence of the low free acidity is not strong enough evidence to throw doubts on this diagnosis in opposition to the persistent blood pictures and clinical condition. It appeared possible at one time that this patient might be developing an aplastic condition following the preliminary pernicious anaemia, and is interesting in that respect since I have described a case of aplastic anaemia having free hydrochloric acid in the gastric juice (131); similar cases with normal gastric secretions have been described by Hurst (1926), Roth and Sternberg (99), and Schmidt (101).

Thus it will be seen that in a series of 208 cases having blood pictures of the primary or Addisonian type eight showed free hydrochloric acid in the gastric contents. Of these eight, two (Cases I and II) were examples of the so-called 'pernicious anaemia of pregnancy' (130); one (Case III) was under observation for fifteen months, had a normal gastric acidity, but typical clinical symptoms and blood pictures of pernicious anaemia; Case IV only showed a small amount of free acid after histamine stimulation, Case V showed a return of small amounts of hydrochloric acid—both were early cases of pernicious anaemia. Case VI, showing similar low acid titres, was diagnosed as early pernicious anaemia-subacute-combined-degeneration of the spinal cord syndrome several months before the onset of a malignant ulceration of the fauces. Case VII had a normal gastric acidity and typical blood count for pernicious anaemia, while the gastric juice, incubated with beef, failed to initiate a remission in another case of pernicious anaemia, thus confirming the diagnosis. Case VIII was originally a typical case of pernicious anaemia, with a very low free acidity; he has shown a delayed response to treatment, suggestive of the aplastic types of anaemia, but there was evidence of bone-marrow activity.

PART II. *Experiments on the Gastric Secretion in Pernicious Anaemia*

A. *Action of histamine on the gastric secretion in pernicious anaemia.* The intense stimulating effects produced by histamine (4- β -amino-ethyl-glyoxaline) upon the gastric secretory glands led Carnot, Koskowski, and Libert (15), and many others (143) to investigate its action in cases with achylia gastrica and with normal secretions.

Katsch and Kalk (64), Faber and Holst (34), Johansen (63), among others, tested the gastric secretion in cases of pernicious anaemia after treatment with liver, and failed to find any return of hydrochloric acid secretion. In general, the consensus of opinion is that histamine furnishes an excellent gastric stimulant whereby many cases, previously considered to be achylia gastrica, may be shown to be pseudo-achylic ones only; on the other hand, patients with pernicious anaemia have true achylia.

For purposes of comparison sixteen of the twenty-five cases of pernicious anaemia that have been investigated after acetylcholine (*vide infra*) were also re-examined after histamine (0.25 to 0.5 mg.) administered subcutaneously in 1 c.c. sterile distilled water. The fractional method of gastric analysis was used, and the following results observed:

Mucus. After histamine stimulation mucus was reduced to negligible quantities, the test samples filtering very quickly (*cf. supra*, p. 363.)

Emptying-time. The average emptying-time of the stomach was 1.9 hours after histamine—maximum 2.75 hours and minimum 1.5 hours—and 1.9 hours in the control tests of these cases. Thus, histamine has no influence on the emptying-time.

Free and total acidities. There was neither alteration in the total acidities nor production of free hydrochloric acid after the use of histamine (except Case IV, p. 372).

Total and mineral (inorganic) chlorides. The effects of histamine on the chloride secretion may be divided into three groups: (a) *Chlorides increased.* Six cases showed marked, and one case slight, increase in the total and inorganic chloride titres (see Table VII, Cases A. B. and W. S.). (b) *Chlorides unchanged.* Eight cases did not show any definite change in the chloride titres, although there was a slower rise in the titre on one occasion than had been observed in the control test (see Table VII, Case A. H.). (c) *Chlorides diminished.* One case showed a reduction in the chloride titres (see Table VII, Case T. F.).

Peptic activities. In these sixteen cases after histamine the peptic activities did not show any alteration from those obtained in the control analyses without histamine. In this connexion it is interesting to recall that Faber and Holst (34) considered that the pepsin content of the gastric juice was increased in nearly all cases, including pernicious anaemia, after histamine. On the other hand, Babkin (3, 4) states that it stimulates the parietal gastric glands, producing increased acid secretion, and only to

a very slight degree are the peptic and mucoid cells affected in the normal animal stomach.

B. *The effect of acetylcholine on the gastric secretion in pernicious anaemia.*
The physiologically active substance, acetylcholine,



was shown to be present in animal tissues by Dale and Dudley (23), although its profound depressant effects on the arterial blood-pressure through its dilator action on the arterioles had been well established long before (22, 24, 58).

Acetylcholine itself is about one-third as toxic as choline, but 100,000 times more active; this is offset by the slower absorption of the former from the tissues when given subcutaneously (126). Whereas the effect of intravenous injection of the salts of acetylcholine in animals is rapid, its effects when administered subcutaneously or intravenously in man are not so dramatic, and it has been successfully employed in the treatment of certain vascular diseases by Villaret and Justin-Besançon. These workers (122) have observed an abundant secretion of pancreatic juice, rich in lipase and amylase, in the dog after acetylcholine. Its stimulating action on the intestines, liver, spleen, submaxillary and lachrymal glands is readily abolished by atropine (22, 58, 123), but, judged by its effect on frog's heart, Clark (19) has demonstrated that this antagonism is one of effects rather than combination.

The influence of acetylcholine on the gastric secretion has already been investigated (129), and it has been shown to have a variable effect in normal subjects; ten out of fourteen cases showed a marked increase in secretion of hydrochloric acid and chlorides, whilst the remainder did not respond beyond the limits of experimental error. Atropine readily abolished or prevented this stimulating action of acetylcholine.

From a consideration of the results obtained in other cases and on normal individuals it was not anticipated that acetylcholine would produce any marked alterations in the gastric condition, especially in view of the fact that histamine had failed to elicit free acid in these cases.

A series of twenty-five cases of pernicious anaemia was examined. In each subject (clinically, typical of severe pernicious anaemia) an ordinary fractional gastric analysis was carried out with the usual gruel meal. In several cases this was repeated—until a complete analysis was obtained with all samples free from bile. Some three to ten days later, the test was repeated, and acetylcholine hydrochloride (0.05 to 0.15 grm.) stabilized in glucose solution was injected subcutaneously fifteen minutes before the first gruel sample was withdrawn. There was little difference in the effects produced by the different doses used.

In the twenty-five cases examined the achlorhydria and low total acidities persisted. The total and mineral chlorides showed certain alterations, and in every case mucus was much diminished after acetylcholine. There were

no alterations in the emptying-times of the stomachs. The results may be considered in three groups.

Group I. Increased chlorides secretion. The twelve cases in this group showed slight to marked increase in the secretions of total (and mineral) chlorides after acetylcholine; ten of these disclosed slight peptic activities in the samples obtained (cf. Table VII, Cases A. B. and W. S.).

Group II. No alterations in chlorides secretion. Twelve cases did not show any alteration in the chloride (total and mineral) secretion or in the peptic activities (Table VII, Case J. P.).

Group III. Diminished chlorides secretion. One case showed a slight fall in total and mineral chlorides, after injections of acetylcholine (Table VII, Case H. H.).

TABLE VII
Total Chlorides

Case.	Test.	Units per 100 c.c. Gastric Juice at 15 minute intervals.									
		$\frac{1}{4}$	$\frac{1}{2}$	$\frac{3}{4}$	1	1 $\frac{1}{4}$	1 $\frac{1}{2}$	1 $\frac{3}{4}$	2	2 $\frac{1}{4}$	2 $\frac{1}{2}$ hours
A. B.	Control	10	3	11	26	32	45	56	42	39	—
	Acetylcholine	8	10	8	11	22	35	68	60	50	—
	Histamine	9	10	12	18	33	48	83	76	68	—
	Liver	8	9	3	15	33	—	—	—	—	—
W. S.	Control	5	5	5	6	9	18	26	26	—	—
	Acetylcholine	11	8	24	35	41	44	48	—	—	—
	Histamine	10	2	3	16	31	33	34	33	—	—
	Liver	5	7	12	19	41	36	31	—	—	—
J. P.	Control	4	4	13	18	24	30	—	—	—	—
	Acetylcholine	1	3	7	12	21	24	—	—	—	—
	Histamine	2	5	13	19	39	30	36	—	—	—
S. W.	Control	6	3	6	3	9	16	27	25	—	—
	Acetylcholine	11	10	9	26	30	33	41	33	—	—
	Histamine	6	4	10	19	34	29	22	24	25	—
	Liver	8	8	11	19	—	—	—	—	—	—
A. H.	Control	10	30	45	46	50	—	—	—	—	—
	Acetylcholine	13	20	34	48	61	57	—	—	—	—
	Histamine	16	14	41	45	50	53	—	—	—	—
	Liver	19	26	38	45	70	—	—	—	—	—
T. F.	Control	2	3	17	27	31	31	37	30	37	33
	Acetylcholine	9	3	10	13	19	—	50	43	52	50
	Histamine	11	5	3	3	15	16	18	21	25	26
	Liver	17	12	9	11	16	24	57	52	51	—
H. H.	Control	15	18	18	34	29	48	53	56	72	71
	Acetylcholine	9	18	19	31	35	39	41	49	53	53

Of two of these cases, one showed increased chloride secretion after histamine but not acetylcholine (Table VI, Case J. P.) and the other after acetylcholine but not histamine; in the latter case, histamine showed a reduced chloride secretion (Table VII, Case T. F.).

C. *Effect of liver and stomach preparations on the gastric secretion in pernicious anaemia.* The remarkable results of liver and stomach in the treat-

ment of cases of pernicious anaemia suggested the possibility of their stimulant action upon the gastric secretory glands. This point has not been investigated except for a few experiments describing the action of fried fresh liver in normal cases only (39, 108). In order to test this a series of fractional gastric analyses were carried out upon ten cases. After an interval of several days following a satisfactory preliminary analysis in each case, the test was repeated with the addition of the particular preparation of liver or stomach. Three commercial preparations of liver extract were used and quantities equivalent to 2-4 ounces were mixed with the one pint of oatmeal—a sample being retained for control analyses.

The test samples obtained usually showed a slight colouration, in the first few samples, when the liver extract was used. The masking of the indicator change during titration was easily overcome by the use of a comparator method.

The stomach preparation employed was a desiccated hog's stomach of which 15 grm., equivalent to approximately 75 grm. fresh whole hog's stomach, was well mixed with the oatmeal gruel (one pint). This had a very strong peptic activity but no free acidity.

In each case analyses were made of the test and control samples for total acidities, total and mineral chlorides, and peptic activities. The results of illustrative cases are conveniently shown in Table VII.

From an examination of these results it will be seen that (a) the achlorhydria was maintained throughout and no free acid appeared in any sample. (b) The total acidities were markedly increased when liver extract was added to the gruel meal, to at least 2-4 times the titre until the stomach had emptied, but there was no alteration after desiccated stomach. (c) The total chlorides did not show any marked alterations—in some cases there was a slight increase, but rather greater than would be accounted for by the chloride content of the added test meal. (d) The emptying-time of the stomach was unaltered, within experimental limits, by the addition of liver extract or desiccated stomach to the gruel.

No peptic activities were obtained after the gruel plus liver extract. The titres obtained with the cases given gruel plus desiccated hog's stomach showed good peptic activities in all the gruel samples (equal to that of the initial hog's stomach-gruel mixture) until the stomach had emptied.

This latter observation is of considerable importance in its bearing upon the deficient digestion and gastric disturbances in pernicious anaemia, and when the frequent occurrence of flatulent dyspepsia in this condition which is relieved by a liver diet and hydrochloric acid and pepsin mixture is recalled (132). It is seen, therefore, that the strong peptic activity of an active hog's stomach preparation used in the treatment of pernicious anaemia should serve as a useful adjunct to the haemopoietic properties of the product—this has been confirmed clinically, since the pepsin-acid mixture can usually be discontinued with this form of therapy.

Summary

1. A series of 208 cases of pernicious anaemia have been examined by the method of fractional gastric analysis and 200 were shown to have achylia gastrica.

2. The fasting contents usually contained considerable amounts of mucus, but no blood, pus, starch, or lactic acid; bile was occasionally found. The average volume was 15.3 c.c., 72 per cent. of cases had fasting contents of less than 21 c.c., and only 2 per cent. exceeded 50 c.c.

3. The average emptying-time of the stomach was 1.6 hours and 85 per cent. had emptied at the end of two hours.

4. The total acidity titres usually lay between 5-10 units.

5. The total and mineral chlorides showed approximately parallel titres; the values varied considerably in different cases, but there was apparently no relationship between them and the clinical condition.

6. The peptic activities of the gastric secretion in pernicious anaemia were negligible.

7. The occurrence of free hydrochloric acid in the gastric secretion of cases of pernicious anaemia has also been discussed, and all the reported cases collected from the literature.

8. Eight cases with free gastric acid have been observed and considered: two were cases of pernicious anaemia of pregnancy; another developed malignant ulceration of the fauces; the remainder were cases of pernicious anaemia and have been discussed.

9. The effects of acetylcholine and histamine on the gastric secretion have been examined in twenty-five and sixteen cases respectively of pernicious anaemia.

(a) No free hydrochloric acid was detected in any sample and the total acidities and peptic activities remained apparently unchanged.

(b) The chlorides in the gastric secretions formed the basis of a division into three groups in which the chlorides were (i) increased, (ii) unchanged, and (iii) diminished. After histamine these groups contained 7, 8, and 1 cases respectively, and after acetylcholine 12, 12, and 1 cases respectively.

(c) The average emptying-time of the stomach was (i) after histamine 1.9 hours (control 1.9 hours), (ii) after acetylcholine 1.75 hours (control 1.6 hours).

(d) Mucus was absent from or negligible in all samples after acetylcholine and histamine.

10. The effects of liver and hog's stomach preparations on the gastric secretion in pernicious anaemia were also investigated.

(a) No free hydrochloric acid was produced in any sample.

(b) The total acidities were increased after liver extracts.

(c) There were only slight increases in the total chlorides.

(d) The emptying-time of the stomach was unchanged.

(e) The peptic activities of all samples after a desiccated stomach-gruel meal were good until the stomach had emptied.

It is a pleasure to acknowledge the co-operation of the Honorary Physicians of the Manchester Royal Infirmary in placing their cases at my disposal for this work.

ADDENDUM.

Since this paper was submitted for publication, another case of pernicious anaemia has been observed having free hydrochloric acid in the gastric juice.

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THE EFFECT OF MASSAGE ON THE METABOLISM OF NORMAL INDIVIDUALS¹

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CONCERNING the effect of massage on metabolism much has been written, but most observers are agreed that there are few, if any, demonstrable changes.

Weir Mitchell (1885), Hirschberg (1887), and Bendix (1894) were among the first to observe an increased flow of urine as the result of massage. Weir Mitchell noted that the total elimination in twenty-four hours was not much altered but that there was a large and abrupt increase within three hours followed by a compensatory decline. An increased urinary output of nitrogen was also noted by Bendix and a few years later by Voight (1896). In 1897-8 an important paper on the effect of muscular exercise, sweating, and massage on metabolism was published by the Edinburgh School (Dunlop, Noël Paton, Stockman, and Maccadam). They observed an increased excretion of water and a slightly increased excretion of phosphorus, but attributed these to the physical influence of the increased lymph flow drawing these from the tissues, believing that they did not indicate any increased katabolism. They considered that their experiment had a negative result. Eccles (1895) believed that the output of uric acid was increased as the result of massage.

The first observations on the effect of massage on the gaseous metabolism were made by Leber and Stüve (1896). Increases of 16.6 per cent. and 8.2 per cent. in the oxygen consumption of fasting subjects were noted during massage, but these values fell a few minutes after its completion. They raise the question of how much reflex contraction of muscle may cause these changes. The slight increases observed were not much greater than were obtained by the simple muscular exercise of bending and stretching the unloaded fingers.

In 1907 Magnus Levy summarized the previous literature on the question of the effect of massage on metabolism and stated that 'slight as the immediate effect of massage is on the interchange of gases and the exchange of heat, so also is its action on the other metabolic processes. The direct effect of massage has been extraordinarily overestimated.'

The use of more modern methods and technique has added but little to our knowledge of massage. Liljestrand and Stenström (1922) applied massage of a moderate nature to one patient and massage of a more severe nature to another. Hyperventilation with a high respiratory quotient was observed

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and appeared to vary according to the type of massage. On the third day of massage a 12 per cent. rise in the oxygen consumption was noted in their first case, but five minutes after the end of the massage period it had declined. The average rise in the second case was 40 per cent. It appears evident, however, that this subject did not remain at rest owing to the severe nature of the massage. On the whole these experiments are unsatisfactory, since involuntary or reflex contraction of muscle occurred as the result of painful stimulation. The relative shortness of their experimental period can also be criticized.

Pemberton and his co-workers (1924, 1927, 1930) have noted an increased volume of urine after the application of massage. Occasionally this amounted to a true diuresis. It may be that this diuresis was due in part to abdominal pressure, as Griffith and Hansell (1925) have suggested. It appears from the work of Bazett *et al.* (1924) that abdominal pressure alone may cause a diuresis. Herxheimer, Kost, and Wissing (1927) believe the diuresis to be referable to a direct effect on the muscular tissues, either mechanical, or through some reflex effect. In contrast to control experiments involving muscle work they found that massage caused a slight increase in the nitrogen output. It is very probable that direct muscular manipulation and the abdominal pressure may act independently. Although they did observe an increased excretion of nitrogen, inorganic phosphate, and sodium chloride more frequently following massage, yet it was not a constant finding. The excretion of creatinine was unaffected and in no case did a creatininuria occur. From a review of the literature and in the light of their own experiments, Pemberton, Cajori, and Crouter conclude that 'massage has no immediate or large effect on metabolism *per se*, but that the cumulative effect which massage nevertheless exercises on the various metabolic processes probably lies in its mechanical influence on the circulation of the parts concerned'.

In 1927 Kost found that the oxygen consumption was not influenced by the employment of massage. Such changes as were found could be attributed to lack of practice and habituation to the massage. On the basis of his work Kost considers that it is improbable that massage *per se* produces a rise in the oxidative processes in the organism. Herxheimer and Kost (1927) carried out a further series of investigations to determine what influence, if any, massage exerted on the oxygen consumption during the recovery phase which follows severe muscle work. Their observations revealed no detectable influence on the oxidation rate or on the recovery time. They hold, therefore, that the action of massage is not oxidative.

From this brief review of the literature, the impression is gained that the great majority of observers have failed to demonstrate any detectable influence of massage on metabolism, with the possible exception of diuresis and an occasional increase in nitrogen output. Even this increased excretion of water and nitrogen has been attributed to the physical influence of the increased lymph flow, and so does not appear to indicate any increased katabolism. Other effects which have been noted have generally been attributed to the reflex movements caused by the manipulations employed—in particular hacking and deep kneading.

General Plan of the Experiments

The general plan of the present series of experiments dealing with the effects of massage on normal metabolism was to measure any changes in the volume and total nitrogen of the urine, and in basal metabolism as determined by oxygen consumption. The subjects were men of average physique and good general health. Standard measurements were taken over a pre-massage period of several days; these were repeated over a second period during which massage was given daily for the time of one hour; and they were continued during the post-massage period of several days in which no massage was used. As control, a similar series of measurements were made with hours of exercise or of complete rest in place of the hour of massage.

Experiment 1. Man: 21 years; height 181 cm.; weight 66 kg.; had been dismissed six months previously with a healed fracture of the tibia. Being now unemployed he offered his services.

Experiment 2. Man: 25 years; height 165 cm.; weight 60 kg.; a University student, voluntarily offered his services. He was in perfect health on admission. During the later days he had a slight 'cold in the head'. This student was also the subject of Experiment 6. The time interval between the two experiments was six months.

Experiment 3. Man: 44 years; height 170 cm.; weight 71 kg.; a seaman, was admitted suffering from a deranged knee-joint. Prior to his operation he was the subject of experiment. He was in perfect health, and apart from occasional locking of his knee-joint suffered no inconvenience.

Experiment 4. Man: 33 years; height 165 cm.; weight 58 kg. An unemployed miner, admitted for a deranged knee-joint, was made the subject of an experiment. The derangement was in all probability a very mild degree of arthritis. There was, however, no coincident wasting or other sign of disease.

Experiment 5. Man: 63 years; height 177 cm.; weight 71 kg.; had fourteen months previously been in hospital suffering from a fractured femur. Union was rapid and satisfactory, but owing to lack of work he had been unemployed for about a year. He was in very good health at the time of admission, walking and cycling being his recreations. During his experimental period he continued his usual walks—about 8 miles each day.

Experiment 6. Same subject as in Experiment 2, again in good physical condition.

Experiment 7. Man: 37 years; height 180 cm.; weight 60.2 kg.; was admitted to hospital in order to have an inguinal hernia radically cured. He was in excellent health apart from this disability and volunteered to act as the subject of a massage experiment prior to operation.

The subjects were allowed to select the quality and quantity of food-stuffs they desired from a prepared list. This intake, as well as the intake of water, was kept as constant as possible. The urine was collected in 24-hourly specimens and preserved with thymol in chloroform. The various

periods during which faeces were collected were marked off with carmine, taken in the form of capsules. The faeces were dried on a steam bath and in an air oven before being analysed. A pre-period of 3-4 days was usually allowed in order to obtain nitrogenous equilibrium. During the experimental period the subjects, except the man in Experiment 5, led a sedentary life in and around the hospital and University precincts. The day's activity in all cases was kept as constant as possible. These men practised breathing with a face mask as soon as they were admitted. The last meal at night was at 7 p.m. The patients emptied their bladders at 8 a.m. and then lay at complete rest in a post-absorptive condition till 9 a.m., when a sample of expired air was taken. Other samples were taken at 10 a.m. and 11 a.m. At 11.15 a.m. the subjects received their breakfast.

The hour between 9 a.m. and 10 a.m., was occupied with rest, massage, or exercise, according to the particular day's programme. During the massage the patient lay as completely at rest as possible, and comfortably warm—room temperature *circa* 19° C. The massage continued for an hour and consisted of general effleurage and deep kneading and squeezing manipulations with passive movements. With the exception of Experiment 6 the collection of expired air was made immediately after the end of the massage. In Experiment 6 the collection (on one day) was made during the last stages of the massage. On the days of exercise certain of the subjects rose at 9.10 a.m., dressed and went for a 30-40 minutes brisk walk, being back in bed again at 10 a.m., when the second collection of expired air was taken. In one case the patient was confined to bed but performed arm exercises. Between the hours of 10 and 11 a.m. the subjects lay at complete rest. On certain of the pre-massage, massage, and post-massage days blood-pressure, by the auscultatory method, and pulse-rate determinations were made at various intervals from 8 a.m. till 11 a.m. On several days the subjects passed urine at 9, 10, and 11 a.m.

The investigation of the effects of massage on the subjects required the daily determination of (1) the total volume and total nitrogen of the urine, and (2) the oxygen consumption at complete rest and in the post-absorptive state, these analyses being made during the pre-massage, massage, and post-massage days. In addition, the oxygen consumption, and the total volume and nitrogen output of the urine were determined immediately following the hour of massage, or control hour of rest or exercise, and also one hour subsequently. Determinations of the pulse-rate were made before, during, and after massage—every 10-15 minutes throughout the three hours. The blood-pressure were also estimated before, immediately after, and one hour after the massage had ended.

The analytical methods employed were the same as those described in previous papers (Cuthbertson, 1929).

Urinary volume. The influence of massage on the urinary volume was investigated from two aspects. The first involved a comparison between

the average total twenty-four hours' elimination of fluid during the pre-massage days with that passed during the period of daily massage, and again with that passed in the post-massage period.

TABLE I
Average Values of 24 Hours in c.c.

State.	Exp. 2.	Exp. 3.	Exp. 5.	Exp. 6.
Pre-massage period	1105 (2 days)	1390 (2 days)	960 (4 days)	952 (4 days)
Period of daily massage	1107 (4 days)	1370 (4 days) 1470 (3 days)	870 (4 days)	921 (5 days)
Post-massage period	1270 (2 days)	—	905 (4 days)	1090 (2 days)

It will be observed that the average daily urinary excretion during the period of daily massage did not differ significantly from the average excretion during the pre-period. Experiment 3 indicated that, as the period of daily massage lengthened, there might be a tendency for a slightly increased output to occur. During the first few days of the post-massage period there was a slightly increased output of urine when compared with the period of massage.

The second aspect of the question of the influence of massage on the urinary volume involved the comparison of the volumes of urine excreted during the hour of massage and the hour immediately following, with the corresponding hourly excretions when the subject was lying quietly in bed or performing walking or other exercise. The subject emptied his bladder at 8 a.m. and again at 9 a.m. In all cases the patient had been lying quietly in bed during the previous twelve to fourteen hours. From 9 a.m. to 10 a.m. the subject lay at rest, or was massaged (in bed), or took exercise, according to the particular experiment. From 10 a.m. to 11 a.m. the patient again lay quietly in bed.

The subject of Experiment 4 was unable to pass urine at 10 a.m., so the 11 a.m. specimen represents the excretion of two hours.

Owing to the fact that basal metabolic determinations were performed just before these specimens of urine were collected, and as the patient generally lay quietly at rest, it is possible that these cases might not have been able to empty their bladders completely in the prone position.

In Experiments 2, 5, 6, and 7 massage produced a greater flow of urine during the hour in which it was performed than during a corresponding hour of light exercise or period of rest in bed. For the hour following the completion of the massage no such definite statement could be made, although the output during this hour on the day of massage generally appeared to be greater than, or almost equal to, that of the corresponding hours of rest or exercise. Comparing the total volumes of urine passed during

the hours of 9 a.m.-11 a.m. in Experiments 2, 4, 5, 6, and 7 the conclusion is reached that massage generally produces, although not constantly and, therefore, not necessarily, an increased elimination of fluid. The two best Experiments, 6 and 7, indicated in the one case (6) that the effect of massage, rest, and exercise produced an equal output of urine during the hours 9-11, and in the second case there appeared to be definite evidence that massage had a greater effect than either rest or light exercise. The subject of Experiment 6 was a student in fine physical training; that of Experiment 7, an unemployed but healthy man.

It would appear that massage produces a more rapid elimination of urine during the hour in which it is performed, but that it may not be a true diuresis, in that it may be compensated by a less rapid elimination in the hour which follows (Experiment 6).

The specific gravity of these urines was not determined in all the experiments. Apart from its regularity, no definite conclusions could be deduced from the available data.

TABLE II

Hourly Outputs, 9 a.m.-10 a.m.; 10 a.m.-11 a.m.

Exp.	Time.	Rest.			Exercise.			Massage.		
		Vol. c.c.	Sp. gr.	T. N. grm.	Vol. c.c.	Sp. gr.	T. N. grm.	Vol. c.c.	Sp. gr.	T. N. grm.
2	9-10	—	—	—	21.0	—	0.276	46.5	—	0.534
	10-11	—	—	—	32.1	—	0.404	35.0	—	0.328
	9-11	—	—	—	53.1	—	0.680	81.5	—	0.862
4	9-11	41	—	0.46	67 (walk)	1.025	0.85	55.5 (aver. 3 days)	1.025	0.57
5	9-10	57	—	0.42	56	—	0.45	98	—	1.21
	10-11	—	—	—	84 (walk)	—	0.56	93	—	0.68
	9-11	—	—	—	140	—	1.01	191	—	1.89
6	9-10	42	1.0174	0.46	35	1.0167	0.43	49	1.0182	0.62
	10-11	44 (aver. 2 days)	1.0183	0.42	49 (walk)	1.0189	0.525	32 (aver. 3 days)	1.0178	0.32
	9-11	86	—	0.88	84	—	0.955	81	—	0.94
7	9-10	73.5	1.0184	0.61	54	—	0.50	100	1.0176	0.69
	10-11	71.5 (aver. 2 days)	1.0197	0.585	72.5 (arm bending and stretching exercises with weights)	—	0.58	83 (aver. 3 days)	1.0173	0.52
	9-11	145	—	1.195	126.5	—	1.08	183	—	1.21

Urinary Nitrogen (Vide Tables II and III). The output of nitrogen was also studied hourly in a manner similar to that just described, and also from day to day before, during, and after massage.

In Experiments 2, 4, 5, 6, and 7 massage produced a greater output of nitrogen during the hour in which it was performed (9. a.m.-10 a.m.) than during the corresponding hour of rest or of light exercise, such as walking or

arm exercises in bed. During the next hour of rest (10 a.m.-11 a.m.) following massage there was generally a smaller amount of nitrogen excreted than during an hour's rest or light exercise. Comparing the total volumes of urine passed during the two hours 9 a.m.-11 a.m., it was found that in only one case (Experiment 5) was there a greatly increased nitrogen excretion resulting from massage. This was coupled with an increased urinary volume. This same subject had also exhibited an increase in an earlier experiment (Experiment 2).

Considering these experiments as a whole, massage appears to cause an immediate increased flow of urine and a proportionally increased excretion of nitrogen. During the hour following massage the effect may persist, or there may be a period of compensation so that the total amount of nitrogen and the total volume of urine passed during the two hours is not significantly greater or less than the relative amounts passed during a corresponding hour of rest or light exercise.

Comparing the total twenty-four hourly outputs of nitrogen in Experiments 2, 3, 4, 5, and 6 during the pre-massage periods, the periods of daily massage, and the post-massage periods, it was observed that with the exception of Experiment 5 there was a slight rise on the first day of massage, but that this rise was not generally maintained. The data during these periods have been averaged in Table III.

TABLE III

Average Values for Urinary Nitrogen grm.

State.	Exp. 2.	Exp. 3.	Exp. 4.	Exp. 5.	Exp. 6.	Average of all Exps.
Pre-massage period	11.51	11.31	11.29	11.68	13.96	11.95
Period of daily massage	12.10 (4 days)	12.17 (first 4 days) 12.66 (next 3 days)	11.07 (4 days)	10.44 (4 days)	13.72 (5 days)	11.90 (4-5 days)
Post-massage period	11.48 (first 2 days) 11.57 (next 3 days)	—	10.55 (2 days)	11.02 (first 2 days) 11.82 (next 2 days)	12.80 (2 days)	11.48 (2 days)

The average values found indicate that in three out of the five experiments massage appeared to cause a slightly decreased excretion of nitrogen. Experiment 5 showed the most definite reduction—an average daily retention of over 1 grm. being found. In two of the experiments a slightly increased excretion of nitrogen was observed which increased still further in Experiment 3 as the massage period was extended.

During the first two days of the post-massage period there was, with one exception, a decrease in the output of nitrogen when contrasted with the period of massage, and in all the cases where this phase was studied the output of nitrogen was also less than during the pre-massage period. The subject (Experiment 5) who did demonstrate a definite increase over the massage period was the one who had exhibited the most definite retention of nitrogen during the period of massage. During the next few days of the post-massage period (Experiments 2 and 5) the values obtained for this period exhibited a return to the pre-massage value.

On taking the mean of the averages of all the experiments the conclusion is drawn that massage when studied over a period of four to five days has no really appreciable effect on the output of nitrogen beyond a very slight tendency to retention which appears to extend into the first day or two of the post-massage period. As has been pointed out individual cases may react differently as, for example, the subjects of Experiments 3 and 5.

It is interesting to note that when the averages of the urinary volumes of all these experiments are also summated and the mean taken there is evidence of a slight decrease in the volume of a fluid passed during the period of massage.

	Vol. c.c.	T. N. grm.
Pre-massage	1102	11.95
Period of daily massage	1051	11.90

Consumption of oxygen. The analytical data will be considered from two aspects. The first is based on a comparison of the average daily values for the oxygen consumption during the pre-massage, massage, and post-massage periods. These observations were made at 9 a.m., the experimental subjects having lain quietly at rest from the previous evening, and being in the post-absorptive condition. They passed urine at 8 a.m. and lay at complete rest during the next hour. (*Vide* Table IV.)

TABLE IV

Average Daily Basal Oxygen Consumption c.c. per Minute

State.	Exp. 1.	Exp. 2.	Exp. 3.	Exp. 4.	Exp. 5.	Exp. 6.	Exp. 7.	Average of all Exps.
Pre-massage period	237 (5 days)	216 (2 days)	225 (4 days)	204 (5 days)	229 (4 days)	226 (7 days)	260 (5 days)	228
Period of daily massage	232 (3 days)	229 (4 days)	217 (7 days)	210 (4 days)	233 (4 days)	232 (5 days)	273 (5 days)	231
Post-massage period	224 (4 days)	—	—	192 (3 days)	233 (4 days)	—	242 (2 days)	

A consideration of the data reveals the fact that massage has but little if any effect on the basal consumption of oxygen. In two of the experiments (2 and 7) there appeared to be a definitely increased utilization of oxygen, but this increase did not exceed 6 per cent. During the post-massage

TABLE V

Exp.	Type of Exp.	State.	O ₂ Consumption per min. c.c.
1	Exercise	At complete rest in post-absorptive state	244
		Lying in bed immediately after completion of 40 minutes' walk	386
		Lying at complete rest 1 hour after walk	259
	Massage (1st day's)	At complete rest in post-absorptive state	241
		Lying in bed immediately after completion of 1 hour's massage	238
		At complete rest 1 hour after massage	244
2	Massage (1st day's) No abdominal massage	At complete rest in post-absorptive state	206
		Lying in bed immediately after completion of 1 hour's massage	230
		At complete rest 1 hour after massage	225
	Massage (abdominal massage included)	At complete rest in post-absorptive state	206
		Lying in bed immediately after completion of 1 hour's massage	207
		At complete rest 1 hour after massage	200
3	Exercise	At complete rest in post-absorptive state	203
		Lying in bed immediately after completion of 40 minutes' walk	216
		At complete rest 1 hour after walk	201
	Massage (average of 3 exps.)	At complete rest, post-absorptive state	211
		Lying in bed immediately after completion of 1 hour's massage	234
		At complete rest 1 hour after massage	229
4	Massage (average of 2 exps.)	At complete rest in post-absorptive state	190
		Lying in bed after completion of 1 hour's massage	209
		At complete rest 1 hour after massage	195
5	Exercise	Lying at complete rest in post-absorptive state	239
		Lying in bed immediately after completion of 40 minutes' walk	253
		At complete rest 1 hour after walk	204
	Rest	At complete rest in post-absorptive state	234
		At complete rest in post-absorptive state (1 hour later)	240
		At complete rest in post-absorptive state (2 hours later)	244
	Massage (average of 3 exps.)	At complete rest in post-absorptive state	234
		Lying in bed immediately after completion of 1 hour's massage	241
		At complete rest 1 hour after massage	218
	6	At complete rest in post-absorptive state	208
		At complete rest in post-absorptive state (1 hour later)	241
		Exercise	247
		At complete rest immediately after walk	296
		At complete rest immediately after walk (1 hour after walk)	228
		Massage (average of 2 exps.)	217
7	Rest	Lying in bed at end of 1 hour's massage	270
		At complete rest 1 hour after massage	241
		At complete rest in post-absorptive state	244
	Massage (average of 3 exps.)	At complete rest in post-absorptive state (1 hour later)	265
		At complete rest in post-absorptive state	249
		Lying in bed at end of 1 hour's massage	268
		At complete rest 1 hour after massage	258

period three out of four of the experiments in which this phase was examined revealed a reduction in the oxygen consumption but not exceeding 7 per cent. Summating the averages of all these experiments during the pre-massage and massage periods (post-massage period not calculated as data less complete), the mean values calculated reveal an increased oxygen consumption of little over 1 per cent.—an insignificant figure when individual fluctuations of ± 15 per cent. may occur normally (Wishart, 1927).

The second aspect of the oxygen consumption which has to be considered, is concerned with the immediate effects of massage and those occurring one hour later. These values are compared with the basal values for the same day and also with corresponding periods of rest and light exercise. In all these experiments the patient passed urine immediately after the collection of expired air was completed, that is at 9, 10, and 11 a.m.

In six out of seven experiments there was an increased oxygen consumption immediately following massage. The level of this increased utilization was not maintained, but declined during the hour which followed to a value generally equal to, or slightly greater than, that existing prior to the application of massage.

Light exercise, such as walking for forty minutes, always definitely increased the oxygen consumption. This increased metabolic level was not maintained during the next hour of rest, but declined.

When the arithmetic mean is taken of the summated average values during these experiments (Table V), it is found that the slight increase in oxygen consumption which appeared to result from massage is not greater than the increase which occurred during a corresponding period of rest.

TABLE VI

Mean Value of Summated Averages of Table V

State.	O ₂ . c.c.	State.	O ₂ . c.c.	State.	O ₂ . c.c.
Immediately before massage (1-7)	221	Immediately before exercise (1, 3, 5, and 6)	233	Resting	229
Immediately after massage	240	Immediately after light exercise	288	Resting	249
1 hour after massage	228	1 hour after light exercise	233		

It is somewhat difficult to explain why there should occur such an increase as the duration of the rest lengthened. The most probable explanation appears to lie in the subject's progressive reaction to the experiment. In the first place it is extremely difficult and requires much self-discipline to lie quite still without falling asleep. In the second place the subject suffers from hunger and is often conscious of abdominal discomfort as his normal breakfast hour passes by.

Pulse-rate. In Experiments 3, 4, and 5 the pulse-rate was determined every fifteen minutes throughout the hour of rest preceding the massage,

then during the hour of massage, and finally during the post-massage hour of rest. In Experiment 5 the pulse-rate was also counted during the three hours of continuous rest. In Experiment 7 the pulse-rate was recorded every ten minutes over the period of three hours. On two of the days an hour of complete rest was substituted for the hour of massage.

TABLE VII

Pulse-rate per Minute

State.	Time. a.m.	Exp. 3.	Exp. 4.	Exp. 5 (a).	Exp. 5 (b).
Pre-massage	8	—	—	67	69
	8.15	—	—	65	69
	8.30	68	61	66	68
	8.45	67	61	66	68
	9.0	67	60	65	69
During massage	9.15	63	61	63	68
	9.30	62	60	61	69
	9.45	62	59	61	69
	10.0	60	59	65	69
Post-massage	10.15	61	59	61	69
	10.30	61	60	61	68
	10.45	62	60	62	68
	11.0	62	60	63	69

Experimental subject 3—average of six days of massage.

4—average of four days of massage.

5 (a)—average of seven days of massage.

5 (b)—average of four days resting without massage.

TABLE VIII

Pulse-rate per Minute

	a.m.	Exp. 7 (a).	Exp. 7 (b).	
Resting	8	62	60	Pre-massage
	8.10	64	60	
	8.20	62	61	
	8.30	62	60	
	8.40	63	60	
	8.50	62	60	
	9.0	62	61	
Resting	9.10	61	60	During massage
	9.20	60	59	
	9.30	60	60	
	9.40	58	59	
	9.50	56	59	
	10.0	57	58	
Resting	10.10	57	57	Post-massage
	10.20	57	57	
	10.30	57	55	
	10.40	57	54	
	10.50	57	54	
	11.0	57	55	

(a) Average of two days where rest substituted for massage.

(b) Average of three days of massage.

The data set out in Tables VII and VIII represent the average values of numerous daily observations in these experiments. It will be observed that there always occurred a slight diminution of one to two beats per minute in the pulse-rate during the hour of massage. During the subsequent hour

of rest there was generally a slight increase of one to two beats per minute. In Experiment 7, however, the rate continued to diminish by other three to four beats per minute.

When comparison is made with the days in which a further hour of rest was substituted for massage it is evident from Experiment 7 that such a decrease as was observed during the hour of massage 9 a.m.-10 a.m. also occurred during complete rest. In the case of Experiment 5, however, there was no alteration throughout three hours of rest, thus constituting a slight difference when compared with the hour of massage.

Taken as a group these experiments indicate that general massage has no definite effect on the pulse-rate. The presence or absence of abdominal massage in the course of the general manipulative procedures appeared to cause no difference in the trend of the pulse-rate. In those experiments where it was applied, the time interval in which it was given corresponded to the period 9.40 a.m.-9.50 a.m.

Arterial-pressures. The means of the summated values for the days of massage are:

	Pre-massage. mm. Hg.	Immediately after massage.	1 hour after massage.
Systolic pressure	106	107	105
Diastolic pressure	73	71	69
Pulse pressure	33	36	36

These figures indicate that massage does not generally alter either the systolic or diastolic arterial-pressures.

The blood-pressure determinations made during corresponding hours of rest and light exercise are insufficient in number to form an accurate basis of contrast.

Discussion

The evidence which these experiments present concerns the reactions of apparently healthy men to general massage. The types of massage employed consisted of stroking, compression, and percussion movements applied in succession to the various parts of the body in the order, lower limbs, upper limbs, chest, abdomen (sometimes omitted), and back. The total period of massage was of fifty to sixty minutes' duration. Both masseurs and masseuses were employed, abdominal massage being omitted when a masseuse was employed.

The investigations were concerned with both the immediate and the more prolonged effects.

The data indicate that massage causes an immediate increase in the output of urine and that this is coupled with an increased excretion of nitrogen. The specific gravity remains fairly constant indicating a proportional increase in the output of total solutes. This increased output of fluid and solutes may be but a temporary acceleration, for, during the hour which follows the period of massage there is sometimes a reduction in both fluid and solutes (including the total nitrogenous compounds) so that when the period of two

hours is compared with the corresponding output during two hours of complete rest, no significant difference can be observed. This increased output of urine appears to be in nature not a true diuresis, but merely a temporary increase in the transport of solute and solvent. These results are in general agreement with the findings of Weir Mitchell (1885), Hirschberg (1887), Bendix (1894), Dunlop *et al.* (1897), Pemberton and his co-workers (1924, 1927, 1930), and also Herxheimer, Kost and Wissing (1927).

This temporary diuresis occurred independently of the application of abdominal massage, and is, therefore, independent of the diuretic effect of abdominal pressure which Bazett *et al.* have noted.

These experiments have demonstrated, further, that in general, massage has no immediate effect on the consumption of oxygen as determined immediately after the completion of the massage, or even during the last few minutes of the finishing manipulations, or after the lapse of one hour. In view of the negative findings of Leber and Stüve (1896) and Kost (1927) such small fluctuations as these observers found could be attributed to excitation of reflex movement caused by the character of the massage employed.

In general no defined effect on the pulse-rate was noted in these experiments.

As stroking, compression, and percussion manipulations were employed fairly rapidly in succession in these cases, the observations of Gopadze (1886) as to the increased rate which results from surface stroking and the decreased rate which results from squeezing and rolling movements could not be confirmed.

The observations on the effect of massage on the blood-pressure indicated that in general there is no alteration in the systolic and diastolic arterial pressures. Edgecombe and Bain (1899) who have investigated the behaviour of the blood-pressure during massage have noted that the arterial pressures were lowered.

Concerning the effect of massage on the total volume of urine and on the total nitrogen output of the twenty-four hourly periods of these experiments, no definite alterations have been found. Such effects as are found are not constant and, therefore, not necessarily an accompaniment of massage. In certain cases there were indications of a definite retention of nitrogen, in others, indications of a slightly increased output when compared with the pre-massage period of relative nitrogen equilibrium. The mean of the summated averages of all the experiments indicated an average retention of 0.05 gm. nitrogen, which can scarcely be held to be indicative of a definitely increased anabolism.

Observations on the basal oxygen consumption also revealed the absence of any decided effect of massage on metabolism.

The present writer is forced to conclude that massage has but little detectable influence on the metabolism of normal individuals as determined by the foregoing methods of analysis. This does not, however, discountenance

massage as a therapeutic agent in abnormal conditions. It is hoped to submit proof of this in a subsequent communication.

Summary

1. General massage applied to normal persons causes an immediate but temporary increase in the output of urine, urinary nitrogen, and total solids generally. This period of increased output may persist in diminished form, but may also be followed by a compensatory decreased formation during the hour which follows the massage.

2. Massage does not appear to produce any definite alteration in the excretion of nitrogen or in the volume output when measured over twenty-four hours in normal persons.

3. Massage has apparently no immediate or delayed effect on the basal consumption of oxygen, pulse-rate, or blood-pressure of normal persons.

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CERTAIN EFFECTS OF MASSAGE ON THE METABOLISM OF CONVALESCING FRACTURE CASES¹

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MUCH has been written concerning the employment of massage in the practice of medicine and surgery, but few metabolic experiments have been performed. Bleibtreu (1887) was one of the first to advocate the use of daily massage for aiding the organism to deal with large quantities of protein. Since then many massage cures have been described. Weir Mitchell (1885) was so convinced of the beneficial results that a charlatan had achieved by the use of general massage, that he employed massage extensively thereafter, particularly to rob his rest cures of their evil. Hale White and Spriggs (1901) made a metabolic study of a case of inanition through worry and neglect. They demonstrated how great may be the retention of nitrogen during the convalescence of such a case. How much of the recovery was due to the two hours' daily massage, and how much was due to other factors are difficult questions to decide.

Few experiments have been performed with any degree of completeness on the effect of massage on the metabolism of muscles atrophied through disuse. Schneider (1928) appears to have made the most satisfactory study. He observed that massage applied to fracture cases, uncomplicated by any general disease, resulted in no increased oxygen consumption. Control experiments with patients performing light weight-lifting movements indicated that even such slight exercise may cause a definite increase in oxygen consumption. These observations on fracture cases are in agreement with the negative results which have been obtained by other workers dealing with normal subjects.

Considering the widespread use of this ancient therapeutic adjunct, it is really surprising that no detectable influence on metabolism has thus far been observed. The present series of experiments represent an extension of the writer's previous observations on normal persons (Cuthbertson, 1932). The aspect to be considered is the influence of massage on subjects whose

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muscles and bones have become atrophied through the disuse which results from injury.

The subjects of some of these experiments were children recovering from osteotomies performed for the correction of bony deformities or from the fracture of bone. The other cases were adults convalescing from the fracture of one or other of the long bones. The methods of feeding and collecting excreta were similar to those employed in the previous paper (1932). Massage in these cases was usually supplemented for the first three days by passive movements, and after that active movements were superadded. These manipulations affected only the joints and soft tissues of the injured limbs—the duration of the massage period being twenty minutes. In most of these cases, the affected limb or limbs were returned to their plaster casings or splints immediately following the period of massage and movement.

The analytical methods were similar to those described in a previous paper (Cuthbertson, 1929).

The experimental subjects will first be described and, since the analytical data are peculiar to the person concerned, they will be described with each case.

TABLE I. *Experiment 1*

State.	Vol. of urine c.c.	Nitrogen grm. total	Sulphur (SO ₃) grm.	Phosphorus (P ₂ O ₅) grm.
32nd day	1000	6.38	1.09	2.01
33rd "	780	6.63	1.09	1.92
34th "	840	6.54	1.09	2.08
35th "	—	6.47	1.15	1.92
1st P.M.	1120	5.46	0.89	1.71
2nd "	1090	5.88	1.01	1.83
3rd P.M. + A.M.	860	5.04	0.79	1.72
4th "	900	5.29	0.76	1.49
5th "	1145	5.04	0.78	1.64
6th "	1130	5.46	1.00	1.85
7th "	950	5.25	0.93	1.85
8th "	990	5.37	0.95	1.71
9th "	1000	4.74	0.78	1.46
10th "	1360	5.00	0.76	1.45
11th "	960	5.21	0.82	1.59
12th "	1340	4.90	0.71	1.49
13th "	1000	5.21	0.94	1.53
Daily intake	—	6.95	—	—

R = Rest.

P.M. = Passive Movement + Massage.

A.M. = Active Movement + Massage.

Experiment 1. This case, a girl, aged 14 years, was admitted to hospital for the correction of 'genu valgum'. Following the operation the patient lay quietly in bed being propped up during the waking hours. Plaster casts were applied later, encasing the legs to well above the knees. On the 32nd day following the operation, collection of urine was commenced and on the 5th day of collection the plaster casts were cut in half and during the entire metabolic period they were only removed for the twenty minutes of daily massage. After the third day of massage, the passive movements

were supplemented by active movements. The extent of the massage was gradually increased, but not the duration. Only the injured area and neighbouring joints were manipulated.

It is obvious from Table I that massage caused in this subject, who was excreting a relatively steady amount of sulphur, nitrogen, and phosphorus, an immediate and definite diminution in the excretion of these metabolites. The S:N ratio of the material stopped being excreted during the 13 days of massage was 1:12.8, being for the first 6 days 1:12.2 and for the last 7 1:13.2. The P_2O_5 :N ratio for this retained material was for the 13 days 1:3.95, for the first 6 days 1:4.4 and the last 7 days 1:3.7.

Experiment 2. This subject, a girl, aged 15 years, also admitted for the correction of 'genu valgum', was subjected to a strictly comparable set of experimental conditions, as was applied to the previous case.

This period of collection commenced on the 82nd day following the operation. The patient was already retaining nitrogen, about 1 gm. per day and the application of massage had little effect, with the exception of a temporary rise in the excretion of nitrogen. Later, however, there was a tendency for an increased rate of excretion to occur. On the 101st day following the accident the patient commenced to menstruate.

TABLE II. *Experiment 2*

	Days.	T.N. gm.	Faecal N. gm. (Average daily excretion).
	82	6.88	
	83	7.14	
	84	6.93	
	85	6.65	
(Massage commenced)	86	6.77	
	87	6.58	
	88	8.40	0.844
	89	8.73	
	90	6.72	
	91	6.72	
	92	6.86	
	93	6.30	
	94	6.93	
	95	7.14	
	96	7.42	
	97	7.98	
	98	7.70	

Daily Intake N. = 8.77 gm.

Experiment 3. This subject, a boy, aged 15 years, was operated on for the correction of 'bow legs'. The immediate metabolic changes have been described in a previous paper (Cuthbertson, 1930; Case 30).

Twenty-seven days after the operation this patient's urine was analysed for nitrogen, sulphur, and phosphorus. The excretion of nitrogen was practically of the same value as during the pre-operation period, the diet having remained constant during both periods. The excretion of sulphur was very slightly lower and that of phosphorus definitely higher than the pre-operation figures. Massage coupled with passive and, after an interval, with active movements caused a temporary diminution in the excretion of all three elements resulting in a retention of sulphur and nitrogen and phosphorus. The S:N ratio of the material stopped being excreted during the period of massage was 1:14.21: the P_2O_5 ratio was 1:3.94.

TABLE III. *Experiment 3*

	Days.	Vol. c.c.	T.N. gm.	T.SO ₃ gm.	T. P ₂ O ₅ gm.
	27	1240	9.76	—	—
	28	1080	8.71	1.84	—
	29	1340	10.39	1.82	3.20
	30	1420	9.95	1.90	2.995
	31	1210	10.08	1.855	2.82
Massage	32	1530	9.02	1.68	2.92
	33	1320	9.61	1.84	2.76
"	34	1010	8.24	1.53	2.36
"	35	1400	9.87	1.82	2.94
"	36	1100	8.92	1.63	2.565
"	37	1070	9.97	1.92	2.645
"	38	990	8.87	1.73	2.30
"	39	1160	9.45	1.87	2.84
"	40	1000	9.34	1.83	2.89
"	41	1120	9.87	1.95	3.09

Daily Intake N = 11.78 gm.

Experiment 4. This subject, a girl, aged 8 years, was admitted to hospital suffering from a fractured femur. On the 40th day following her accident the experimental period was commenced. This case appeared to be retaining nitrogen prior to the imposition of massage. Massage caused no apparent change at first, but as the period lengthened a slight retention occurred.

TABLE IV. *Experiment 4*

	Days.	T.N. gm.
	40	8.89
	41	6.16
Massage	42	6.125
	43	6.02
"	44	6.02
"	45	5.915
"	46	6.19
"	47	5.88
"	48	5.32
"	49	4.62
"	50	5.18
"	51	5.145

Daily Intake of N. = 8.11 gm.

Experiment 5. This case, a boy, aged 10 years, was massaged from the 37th-43rd day following the accidental fracture of his right femur.

Massage resulted in a slight increase in the excretion of nitrogen. Prior to the imposition of massage, however, he was definitely retaining nitrogen.

TABLE V. *Experiment 5*

	Day.	T.N. gm.
	35	7.45
	36	7.45
Massage	37	7.35
"	38	8.08
"	39	7.66
"	40	7.98
"	41	8.19
"	42	7.77
"	43	7.76

Daily Intake of N = 10.16 gm.

The concluding data concern the effect of massage on adults with fractured long bones.

Experiment 6. The experimental subject was a man, aged 51 years, who was admitted to hospital suffering from a fractured femur.

Three weeks after the accident he was subjected to a massage experiment. The splint was reapplied after the hourly period of massage. On the 6th day of massage the splint was removed and the leg was loosely held between sand pillows thereafter.

On the application of massage to this case little change occurred, but a retention of nitrogen followed the freeing of the affected limb from the splint.

TABLE VI. *Experiment 6*

	Day.	T.N. grm.
	18	13.65
	19	13.33
Massage	20	13.23
	21	12.91
"	22	13.33
"	23	12.39
"	24	12.81
"	25	14.38
"	26	12.91
"	27	12.39
"	28	12.28
"	29	12.60
"	30	12.49
"	31	12.07

Experiment 7. The subject of this experiment was a woman, aged 56 years, who had fractured her left femur.

Massage was commenced on the 46th day following the injury. The general manipulative procedures employed in massage were supplemented with active and passive movements from the start. The splint was not reapplied.

TABLE VII. *Experiment 7*

	Day following injury.	T.N. grm.
	44	8.92
	45	8.71
Massage	46	7.14
"	47	7.14
"	48	7.77
"	49	8.61
"	50	7.45
"	51	7.35
"	52	6.19
"	53	7.24

In this experiment there was a decided diminution in the urinary excretion of nitrogen as the result of massage and movement, and this commenced on the first day of application.

Experiment 8. This case, a man, aged 59 years, suffered from a fracture of both bones of the left leg. On the 42nd day after the injury he was submitted to a massage experiment.

The course of massage was supplemented with passive movements from the start.

The data reveal but a slight reduction in the urinary output of nitrogen as the result of massage.

TABLE VIII. *Experiment 8*

	Day following injury.	T.N. grm.
	40	12.88
	41	12.74
Massage	42	12.46
"	43	11.34
"	44	12.74
"	45	13.44
"	46	11.48
"	47	12.04
"	48	11.76
"	49	12.18
"	50	10.92

Experiment 9. This patient, a man, aged 34 years, was massaged from the 34th to 37th days following the fracture of a tibia. During the 38th day he had no massage. Then occurred two further days of massage, then two days without.

TABLE IX. *Experiment 9*

	Day following injury.	T.N. grm.	
	33	14.42	(3rd of diet)
Massage	34	14.00	
"	35	13.08	
"	36	11.23	
"	37	11.74	
No massage	38	11.33	
Massage	39	12.15	
"	40	11.74	
No massage	41	11.12	
"	42	10.81	
"	43	11.43	
"	44	11.12	

Daily intake of N = 15.39 grm.

The effect of the massage or movements caused a retention of N which persisted after these procedures had ceased.

Discussion

These experiments which have been enumerated, have all been concerned with the study of the reaction to massage of individuals of varying ages who had been convalescing from a breach of continuity of one or more of the long bones of the lower limbs either through accident or by surgical intent.

The experiments were commenced long after the initial effects of the injury had worn off. Table X contains the average daily urinary output of nitrogen during 1-4 days of the pre-massage period, and also the daily average excretion during the period of massage.

A well-defined decreased elimination of nitrogen was noted in seven out of the nine experiments. Both the exceptions were adolescents. The average

daily decreased elimination, in reality an increased retention, varied from 0.59 grm. to 2.62 grm. in the adult series, experiments 6-9, with an average value of 1.36 grm. per day. In the younger series the retention varied from 0.55 grm. to 1.30 grm. per day. In the two cases who exhibited a slightly increased nitrogen output, varying from 0.35 grm. to 0.50 grm., there was evidence that this increased elimination was really a diminished retention as these individuals were generally storing nitrogen prior to the superimposition of massage.

TABLE X

Period.	Exp. 1.	Exp. 2.	Exp. 3.	Exp. 4.	Exp. 5.
Average daily N excretion prior to massage	6.505 (4 days)	6.90 (4 days)	10.01 (2 days)	6.14 (2 days)	7.41 (3 days)
Average daily excretion of N during massage	5.36 (1-6) 5.10 (6-13)	7.25 (1-13)	9.32 (1-10)	5.59 (1-9)	7.91 (1-6)
Average daily decrease or increase in N output	-1.145 (1-6) -1.405 (6-13)	+0.35	-0.69	-0.55	+0.50
Period.	Exp. 6.	Exp. 7.	Exp. 8.	Exp. 9.	
Average daily N excretion prior to massage	13.28 (2 days)	8.815 (2 days)	12.81 (2 days)	14.42 (1 day)	
Average daily excretion of N during massage	12.69 (1-11)	7.36 (1-8)	12.04 (1-9)	11.80 (1-11)	
Average daily decrease or increase in N output	-0.59	-1.455	-0.77	-2.62	

The evidence of these experiments indicates that massage, even without active movement on the patient's part, and limited to but 20 minutes in the day, is yet sufficient to cause a definite acceleration of the anabolic processes even when the injured member is returned to its splint and thus rendered immobile for another 23 hours 40 minutes (vide Experiment 1).

Although nitrogen has been most fully studied, the evidence of Experiments 1 and 3 indicates that the output of sulphur and phosphorus is similarly affected. The S:N ratio of the material stopped being excreted in Experiment 1 was 1:12.8 for the period of 13 days. During the first 6 days it was 1:12.2, and during the last 7—1:13.2. These ratios suggest a deposit of some sulphur rich material. It may be muscle, but the generally accepted ratio for muscle is somewhat lower 1:14-1:15. In Experiment 3, however, the S:N ratio of the material stopped being excreted was that of muscle, viz. 1:14.21. It may be that had the experimental period of Case 1 been prolonged, evidence of a closer proximation to the S:N ratio of muscle might have been to hand as there are indications that the sulphur moiety tends to be mobilized more rapidly than nitrogen.

The P_2O_5 :N ratios of the material retained in Experiments 1 and 3 indicate that phosphorus is probably being stored in bone as well as in muscle, for the ratio in Experiment 1 was 1:4.02, and for Experiment 3 1:3.94. The P_2O_5 :N ratio of muscle was found by Munk (1893) to be 1:6.8, a much lower ratio than that found in the above experiments.

Massage, therefore, when applied locally to the area of wasted tissue which results from injury and immobilization, causes generally, though not constantly, an increased anabolism of muscle and also of bone.

The chief value of massage in convalescing fracture cases probably is in facilitating the passive and active movement of stiff joints. From the writer's previous observations on normal subjects (Cuthbertson, 1932), and from the present observations, facility of movement is probably of greater benefit than much massage.

Summary

1. Massage supplemented by passive movement, when applied even for 20 minutes per day, to patients convalescing from fractures of the long bones, causes generally, but not constantly (seven out of nine experiments), a decreased urinary excretion, in effect, an increased retention of nitrogen, sulphur, and phosphorus.

2. Judged by clinical evidence and by the evidence of the S:N, P_2O_5 :N ratios of the material stopped being excreted, muscle and bone appear to be the tissues chiefly affected by this anabolic activity.

I wish to thank Professor E. P. Cathcart for his interest in this work. I am also indebted to Dr. Edwards, Massage Officer, for his co-operation.

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ALEUKAEMIC MYELOSIS OF THE LEUCOPENIC TYPE, CLINICALLY SIMULATING CHRONIC APLASTIC ANAEMIA¹

By F. PARKES WEBER

MANY cases clinically diagnosed as aplastic anaemia have doubtless really been examples of *aleukaemic lymphadenosis* or *aleukaemic myelosis*, generally with a leucopenic blood picture.

The following case, which I shortly communicated to the Association of Physicians (Sheffield Meeting, May 22, 1931) as one of aplastic anaemia, was proved by the subsequent post-mortem examination to be one of *leucopenic aleukaemic myelosis*, that is to say, of the same nature as myeloid leukaemia, but with decrease instead of increase in the total number of leucocytes.

Present Case

The patient, J. T., aged 31 years, a well-built man, was admitted to hospital on February 18, 1931, in an exceedingly anaemic condition, with a blood count as follows:—Haemoglobin 20 per cent.; erythrocytes 770,000; colour-index 1.3; leucocytes 4,900. The history was that he had had 'influenza' in September 1930, and that since early January 1931 he had suffered from gradually increasing pallor with slight bleeding from the gums. He had not had a sore throat or sore tongue, and had not felt 'really ill'. There was nothing else of consequence in the history obtained.

On admission to hospital there was no fever. No enlargement of spleen or liver or superficial lymphatic glands; no purpura. There was an 'anaemic' murmur at the left base of the heart. The blood-serum gave negative Wassermann and Meinicke reactions, and a very weakly positive indirect Hijmans van den Bergh reaction for bilirubin. Brachial blood-pressure: 120/55 mm. Hg. Urine: specific gravity 1.015; acid; free from albumin and sugar and excess of urobilinogen. No gastric achlorhydria (fractional tests). Perivascular retinal haemorrhages of various sizes were present over the whole fundus of both eyes.

The treatment in the hospital consisted almost entirely in repeated blood transfusions. Very small intravenous injections of neosalvarsan were given at first, but were discontinued in April. A liver preparation and a liver diet and—for a short time—a gastric mucosa preparation were tried, with negative result. The result of blood transfusions seemed good in regard to the general condition of the patient, and in June and July 1931, when

¹ Received May 2, 1932.

the blood transfusions were repeated at short intervals, the erythrocyte count (July 13) reached 4,600,000 (leucocytes 4,200). About that time the patient felt well and was up the whole day without getting tired. The retinal haemorrhages almost disappeared. But he sometimes suffered from oozing of blood from the gums, and in August developed swellings over the right upper maxilla, the right mastoid and some of the ribs, together with haemorrhagic pleural effusion on the left side, which had to be tapped. The oozing of blood from the gums very much increased. In September there was a gangrenous condition of the gums on the right of the upper jaw. He died on September 21, 1931. At the end of August and in September there was often fever to about 100° F. Previously fever had been mostly in connexion with blood transfusions, of which (thanks to the generous Red-Cross donors) he had no fewer than thirty-seven. Rigors were avoided in connexion with the later blood transfusions by the employment of the 'athrombit' direct method (1) (300 c.c. each time). For help in the treatment and examination of the case I have especially to thank my house-physician at that time, Dr. M. Scholtz.

The table on pp. 412-13 comprises most of the blood counts, at all events, those more complete. It should be noted that many of them were specially taken to check the result of blood transfusions, or in regard to oozing of blood from the gums, &c. The thrombocytopenia, which was present throughout, doubtless helps to explain the haemorrhagic tendency, which became extreme towards the end, and was the final cause of death.

Necropsy and Microscopic Examination

The body was that of a young man normal in general and sexual development. There were (doubtless recent) purpuric spots on the lower extremities and some other parts. The examination of the viscera confirmed the final great increase in the haemorrhagic tendency:—blood effused on both sides in the thorax; petechiae on the pleurae, pericardium and peritoneum and on the surface of the kidneys, in the gastric mucosa, &c. The following data were noted:—*Heart*: weight 350 gm. There were some flattish white nodules (up to diameter of a sixpenny piece in size) on the pericardial surface of the left auricle, and in the right auricle about the insertion of the tricuspid valve there was a similar nodule. *Liver*: weight 2,200 gm.; definitely enlarged. *Spleen*: weight 400 gm.; enlarged and somewhat soft. At the hilum of the spleen were what seemed to be some small splenunculi. Some of the mediastinal, retroperitoneal and mesenteric lymphatic glands were red, and a red pea-sized nodule on the left side of the thorax was a lymphatic gland (as the microscopic examination showed). There were nodular haemorrhagic parosteal swellings over the third left and some other costo-chondral junctions, a hard nodule over the front of the sternum, and some parosteal thickening over the right upper maxilla.

The bone-marrow in the right femur was examined and found to be chocolate-coloured throughout.

Microscopic examination. Sections were stained with haematoxylin and eosin, and duplicates with Giemsa's stain.

The marrow from the middle of the shaft of the femur consists almost entirely of closely packed uninuclear cells with fairly large nuclei, very few fat vesicles remaining. Amongst these cells is a good deal of pigment, doubtless haemosiderin, probably a result of the repeated blood transfusions

and of the terminal severe haemorrhagic 'diathesis'. Unfortunately no blood films for the oxydase reaction were taken at the time of the necropsy, but I think it may be accepted as most probable that the cells in question are chiefly myeloblasts; there are also definite eosinophile cells amongst them; one or two cells are seen in mitosis.

The parosteal swelling over the right upper jaw consists mainly of similar cells to those in the bone-marrow. One of the nodules from the heart (see above) has been likewise examined and is found to be an infiltrate of similar nature. In the spleen the Malpighian bodies are relatively small and the pulp is increased by cells of the same kind as those in the bone-marrow. In the liver similar cells occupy the blood-capillaries between the columns of liver cells, but are not aggregated in the interlobular spaces. In the kidney there is patchy infiltration with similar cells. I think there can be no doubt that the infiltration of these viscera is of the nature of a true myelosis. I have to thank Dr. A. Piney for looking through some of the sections with me.

Discussion

This case of myelosis, which was continually under observation from nearly the beginning of the illness, was not only aleukaemic—that is to say, the total leucocyte count scarcely ever exceeded the normal—but was also almost permanently leucopenic, since the total leucocyte count was nearly always below the normal. Accompanying the terminal gangrenous stomatitis, &c., at the end, there was a slight increase in the leucocyte count.

The use of the terms *myelosis*, for myeloid leukaemia, and *lymphadenosis*, for lymphoid (lymphatic) leukaemia, is undoubtedly convenient, as it enables one to qualify cases as aleukaemic or leucopenic, in which the total leucocyte count is temporarily or permanently not above the normal (aleukaemic myelosis and aleukaemic lymphadenosis) or temporarily or permanently below the normal (leucopenic myelosis and leucopenic lymphadenosis), without using self-contradictory terms, such as aleukaemic or leucopenic leukaemia.

Leucopenic myelosis and leucopenic lymphadenosis may clinically simulate aplastic anaemia, as the above-described case did, when the red blood picture is of the non-regenerative type, but they may somewhat simulate pernicious anaemia when the red blood picture shows the presence of megaloblasts and other nucleated red cells, as well as poikilocytosis and polychromasia. This was so in a case (2) I described in the *Transactions of the Pathological Society of London*, in 1904, under the heading 'leukanaemia'. Later on, in 1914, H. Hirschfeld (3), of Berlin, when he established the term 'aleukaemic myelosis' (apparently suggested by Hermann Schridde in 1910), stated that this case of mine might be regarded as a good example of what he meant by the term in question.

That middle-aged patient, whose illness had commenced a year previously, was somewhat fat, and had the puffy, pale, sallow appearance met with in cases of true pernicious anaemia. But the liver and spleen were greatly and uniformly enlarged and the visceral changes discovered at the post-mortem examination were certainly of leukaemic nature.

Blood Counts

	Feb. 18.	Feb. 23.	March 2.	March 9.	March 20.	March 30.
Haemoglobin per cent.	20	25	—	20	24	19
Erythrocytes per c.mm.	770,000	894,000	880,000	940,000	1,500,000	1,014,000
Colour-index	1.3	1.4	—	1.06	0.8	0.94
Leucocytes per c.mm.	4,900	16,400	—	4,900	9,500	3,350
Myeloblasts per cent.	—	—	—	18	24	20
Myelocytes per cent.	—	—	—	4	5	5
Metamyelocytes per cent.	—	—	—	2	0	1
Polymorphonuclear neutrophils per cent.	—	—	—	22	11	17
Lymphocytes per cent.	—	—	—	48	58	53
Monocytes per cent.	—	—	—	6	2	4
Eosinophils per cent.	—	—	—	0	0	0
Basophils per cent.	—	—	—	0	0	0
Reticulocytes	—	—	—	—	—	—
Nucleated red cells to 100 leucocytes	—	—	—	—	—	—
Thrombocytes per c.mm. of blood	—	16,198	50,000	—	0	0
Anisocytosis	—	—	—	—	+	+
Poikilocytosis	—	—	—	—	0	+
Polychromasia	—	—	—	—	0	0
Positive oxydase reaction per cent. of leucocytes	—	—	—	—	—	—

	April 2.	April 9.	April 13.	April 14.	April 18.	April 24.
Haemoglobin per cent.	24	20	30	—	30	20
Erythrocytes per c.mm.	1,200,000	1,220,000	1,640,000	—	1,520,000	1,020,000
Colour-index	1.0	0.82	0.91	—	1.0	1.0
Leucocytes per c.mm.	4,800	4,900	4,900	—	4,100	3,800
Myeloblasts per cent.	26	12	39	—	13	26
Myelocytes per cent.	6	2	2	—	3	6
Metamyelocytes per cent.	1	3	0	—	0	2
Polymorphonuclear neutrophils per cent.	12	9	18	—	17	9
Lymphocytes per cent.	54	72	36	—	67	52
Monocytes per cent.	1	2	5	—	3	5
Eosinophils per cent.	0	0	0	—	1	0
Basophils per cent.	0	0	0	—	0	0
Reticulocytes	—	—	—	—	—	—
Nucleated red cells to 100 leucocytes	0	0	0	—	0	0
Thrombocytes per c.mm. of blood	—	—	one found	—	0	very few
Anisocytosis	+	+	—	—	0	+
Poikilocytosis	0	0	—	—	0	+
Polychromasia	0	0	—	—	0	0
Positive oxydase reaction per cent. of leucocytes	—	—	—	74	—	—

Haemoglobin per cent.

April 27.
29May 1.*
24May 8.
19May 19.
24May 26.
24June 2.
22

	April 27.	May 1.*	May 8.	May 19.	May 20.	June 2.
Haemoglobin per cent.	29	24	20.	19	24	22
Erythrocytes per c.mm.	1,100,000	1,340,000	940,000	980,000	1,500,000	1,160,000
Colour-index	1.32	0.9	1.06	1.0	0.8	1.0
Leucocytes per c.mm.	4,400	2,800	6,700	2,700	3,650	3,850
Myeloblasts per cent.	33	34	31	30	42	36
Myelocytes per cent.	4	4	14	4	4	7
Metamyelocytes per cent.	0	2	1	0	0	2
Polymorphonuclear neutrophils per cent.	11	14	9	5	12	18
Lymphocytes per cent.	47	44	43	59	37	44
Monocytes per cent.	4	2	2	1	2	1
Eosinophils per cent.	1	0	0	0	0	0
Basophils per cent.	0	0	0	0	0	0
Reticulocytes	—	a few	—	—	—	—
Nucleated red cells to 100 leucocytes	0	0	0	0	0	0
Thrombocytes per c.mm. of blood	0	very few	—	very few	very few	—
Anisocytosis	—	+	—	+	+	+
Poikilocytosis	—	+	—	+	+	+
Polychromasia	—	0	—	0	0	0
Positive oxydase reaction per cent. of leucocytes	—	—	—	—	75	—

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	June 18. †	June 26. †	July 13. †	July 22. †	August 24.	Sept. 11.	Sept. 19.
Haemoglobin per cent.	49	62	78	80	—	38	38
Erythrocytes per c.mm.	2,012,000	2,640,000	4,600,000	4,410,000	—	1,780,000	1,725,000
Colour-index	1.21	1.17	0.85	0.91	—	1.07	1.1
Leucocytes per c.mm.	4,900	3,750	4,200	3,000	—	12,350	9,950
Myeloblasts per cent.	37	23	—	—	45	40	34
Myelocytes per cent.	5	6	—	—	11	11	9
Metamyelocytes per cent.	4	3	—	—	1	0	1
Polymorphonuclear neutrophils per cent.	18	26	—	—	14	19	34
Lymphocytes per cent.	36	41	—	—	27	22	22
Monocytes per cent.	0	1	—	—	1	6	0
Eosinophils per cent.	0	0	—	—	0	1	0
Basophils per cent.	0	0	—	—	1	1	0
Reticulocytes	a few	0	—	—	—	—	—
Nucleated red cells to 100 leucocytes	0	0	—	—	0	0	0
Thrombocytes per c.mm. of blood.	very few	very few	—	—	—	one or two	—
Anisocytosis	0	+	—	—	—	+	—
Poikilocytosis	0	0	—	—	—	0	—
Polychromasia	0	0	—	—	—	0§	—
Positive oxydase reaction per cent. of leucocytes	70	—	—	—	72	—	—

* Before subcutaneous injection of 1 c.cm. of 1-1,000 adrenalin solution; and three differential leucocyte counts at five-minute intervals afterwards. It should be noted that these differential counts suggested an aplastic condition of the haemopoietic bone-marrow ('adrenalin-test' after Bercetold).

† Here the trial of repeated blood-transfusions at short intervals was in progress.

§ One or two erythrocytes showed punctate basophilia on September 11.

Cases of aleukaemic myelosis and aleukaemic lymphadenosis with parosteal nodular infiltration are doubtless closely allied to those cases of chloroma, in which the blood picture shows no excess of white cells or a definite leucopenia; and such cases of chloroma may by the oxydase reaction be divided into a myelosis group and a lymphadenosis group, that is to say, into a chloromyelosis group and into a chlorolymphadenosis (Lehndorff) group.

At one time I thought that the present case would turn out to be similar to the remarkable one of a man, aged 30 years, demonstrated by A. F. Hurst and C. F. Cosin at the meeting of the Medical Section of the Royal Society of Medicine, at Guy's Hospital, on November 25, 1930, and described by R. Stewart Harrison in 1931, under the heading, 'A Case of Primary Aplastic Anaemia, treated with 105 blood transfusions in four years' (4). But in blood counts from the latter case primitive forms of white cells were apparently not observed and the clinical course was different. A histological ('biopsy') examination of a little piece of bone-marrow from the sternum showed that in that case the red bone-marrow was not replaced by fat, as in supposed classical examples of aplastic anaemia.

The examination of the leucocytes in blood films by the oxydase reaction was obviously of especial diagnostic importance in my case, though at first I thought that the relative abundance of the myeloblasts and myelocytes in the blood counts might be explained as a peculiar reaction resulting from the neosalvarsan treatment, and the blood transfusions. It should be noted also that a certain degree of myeloid hyperplasia may be present in the bone-marrow in agranulocytic cases (5). It should also be specially noted that, according to those who maintain that 'myeloblasts' cannot give any positive oxydase reaction, most of the cells that we have counted as myeloblasts should be termed 'immature myelocytes'.

In connexion with the present case I would quote one of N. Rosenthal's conclusions (6) regarding the differentiation of cases of aplastic anaemia and agranulocytosis from leucopenic myelosis:—'Leucopenic myeloid leukaemia may symptomatically resemble some of these blood conditions, but the constant presence of the characteristic myeloblasts and myelocytes or lymphoblasts in the peripheral blood is important for the differentiation of this particular disease.'

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AFTER-HISTORY OF ARTIFICIAL PNEUMOTHORAX: COMMENTS ON 91 SUCCESSFUL AND 31 UNSUCCESS- FUL CASES¹

By RICHARD R. TRAIL and GEORGE D. STOCKMAN

(From King Edward VII Sanatorium, Midhurst)

BETWEEN October 1924 and December 1930 artificial pneumothorax was attempted in 122 cases. All have been followed up in the records of the Sanatorium till December 1931, and so have an after-history of from one to seven years from the date of attempted induction of the treatment.

In ninety-one cases induction was successful, and these are considered in this inquiry under the heading 'Successful Cases'. Of the remaining thirty-one, no pleural space, or only a small pocket, was found in twenty, while in eleven the treatment had to be abandoned after a few refills because of the presence of gross adhesions which militated against collapse of the lung. These thirty-one are further considered under the heading of 'Failures'. In many of the successful cases there were adhesions present, but these did not interfere with efficient collapse of the lung, and if the patient was still on refills at the time of discharge from the Sanatorium, which, on an average, was six months after the induction of the treatment, the case was considered as successful for the purposes of this investigation into after-history as to the value of the treatment.

For comparison with the results of treatment as set out in the recent publication on the after-history of Sanatorium-treated patients (1) all cases have been grouped in accordance with the following definitions:

Group 1. Disease of slight severity, limited to small areas of one lobe on either side, which, in the case of affection of both apices, does not extend beyond the spine of the scapula or the clavicle, or in the case of affection of the apex of one lung, does not extend below the second rib in front.

Group 2. Disease of slight severity, more extensive than Group 1, but affecting at most the whole of one lobe; or severe disease extending at most to the half of one lobe.

Group 3. All cases of greater severity than Group 2, and all those with considerable cavities.

Reference to Table A will show that only fourteen of the 122 cases are entered as 'Advanced', and it is necessary to point out that no case

¹ Received May 4, 1932.

considered for pneumothorax was one of 'slight severity'. All were positive sputum cases and were selected for collapse therapy usually because the infiltration was of an acute and active type demanding interference, and in all Sanatorium treatment on accepted lines of rest up to absolute bed rest had failed after a reasonable trial, varying according to the type of case and the wishes and circumstances of the patient.

At the time of attempted induction, each case was allotted to one of three categories called 'Choice', and although this may be open to the criticism of 'begging the question' as based on a forecast of the likelihood of benefit, it was hoped to find a criterion for prognosis founded on the extent and type of disease judged by physical and X-ray findings. These 'Choices' may be defined as follows:

Choice I. Cases with recent involvement of one lung.

Choice II. Cases of longer-standing disease in one lung, e.g., with evident fibrosis or cavitation.

Cases with less extreme disease in the lung chosen for treatment, but with involvement of the other lung not beyond the upper third.

Choice III. Cases with bilateral disease, but with a possibility of aid by limited pneumothorax on the more active side, e.g., such cases *in extremis* from haemorrhage.

If these 'Choices' be applied to the after-histories, the following table emerges:—

TABLE I. *After-history of Cases Successfully Induced*

	Alive.		Dead.	Totals.
	T.B. +	T.B. —, or no sputum.		
Choice I	4	33	2	39
Choice II	9	27	10	46
Choice III	3	—	3	6
	16	60	15	91

The table shows that of 39 Choice I cases, 37 (95 per cent.) are still alive, and of these, 33 (89·2 per cent.) are T.B. —, or have no sputum; of the 46 Choice II cases, 36 (78·3 per cent.) are alive, and of these, 27 (76 per cent.) are T.B. —, or have no sputum; while only 3 (50 per cent.) of the 6 Choice III cases are alive and all 3 are T.B. +.

It would therefore appear that Choice I cases have a definitely better prognosis than Choice II, and that the treatment in Choice III cases can be no better than palliative.

There is also shown that of the 91 successfully induced, 76 (83·5 per cent.) are alive in from one to seven years, and that of the 76, 60 (79 per cent.) are now T.B. —, or have no sputum.

Seventy-six of the ninety-one cases are still alive; forty-eight of them have now ceased to have refills; the remaining twenty-eight are still on treatment. These groups are considered separately in Tables II and III. Table II sets out the results in the forty-eight cases who have stopped refills.

TABLE II. *Cases Ceased Refills and Still Alive*

	Side.		Choice.			Fluid.	Larynx.		Sputum.		Total.
	L.	R.	I.	II.	III.		Healed.	I.S.Q.	T.B.+	T.B.— or no sputum.	
Completed treatment	18	11	13	16	—	13	5	—	—	29	29
Re-expanded	3	—	2	1	—	—	—	—	—	3	3
Obliterated after fluid	6	4	6	3	1	10	2	1	4	6	10
Re-expanded for advancing disease in other lung	1	2	2	1	—	1	—	—	2	1	3
Stopped for pyo-pneumothorax	1	2	—	2	1	3	—	—	3	—	3
Total	29	19	23	23	2	27	7	1	9	39	48

Under the heading 'Completed Treatment' are counted those who continued refills until it was considered safe to allow re-expansion of the lung, and in no case was this under three years from the time of induction, so that all the twenty-nine have an after-history of not less than three years and up to seven years. All the twenty-nine are to-day T.B. —, or have no sputum, and are well and fit for work. It is of interest that thirteen of them had a hydropneumothorax (*vide* heading 'Fluid') at some time during the course of the treatment, and that it did not interfere with the present excellent result of the pneumothorax. One case developed an ischiorectal abscess during the treatment, and one tuberculous disease of the pelvis; both are now healed. In two cases, both with left-sided pneumothorax, phrenic evulsion was performed, as with re-expansion there occurred displacement of the heart and mediastinum and loss of weight; both have done well since. Five cases had laryngeal tubercle and all are healed; four had this complication prior to the induction of treatment, but one developed it while under the treatment and still in the Sanatorium, and required the application of the electro-cautery by Sir St. Clair Thomson to produce healing. Reference to the effect of artificial pneumothorax on laryngeal tubercle was made in a previous article (2).

'Re-expanded' cases include those in whom it was impossible to continue the treatment as the lung expanded in spite of attempts to keep it collapsed. Three come under this heading, and it is of note that one only required no further treatment; in the other two sputum returned and was again positive after having been negative for two years, and while in one a course of Sano-crysin given two years ago was sufficient to produce negative sputum, the other had to go on to phrenic evulsion and thoracoplasty by Mr. Tudor Edwards a year ago. All three are well and fit for work.

Ten cases 'obliterated after fluid', that is, the pleural cavity closed up after a complicating hydropneumothorax, and while six are now T.B. — the other four are again or still T.B. +. One of the T.B. — cases is worthy of note. While under treatment in 1928 with a left-sided pneumothorax, acute appendicitis necessitated operation; on return to the Sanatorium

a hydropneumothorax of the left side was found and very active disease of the right upper lobe. A right-sided pneumothorax was induced in early 1929 and then, while the left was obliterating, fluid appeared in the right pleural cavity; this also obliterated in early 1930. Laryngeal tubercle was present on admission and is now healed; at present there is no cough and the patient is fit for light work.

Three cases have been re-expanded for 'disease on the other side'. One has done well and is T.B. - and working; the remaining two are still positive, though one has now a pneumothorax on the other side, and the other has had phrenic evulsion and Sanocrysin but is still very ill.

Three cases have had to be abandoned for 'pyopneumothorax'. While all three are T.B. + one is in good condition, though originally a Choice III case with much disease in the better lung. One is in poor condition, the third has had phrenic evulsion and the first stage of thoracoplasty and reports marked improvement. It is probably unnecessary to add that all cases that have not gone on to completion of pneumothorax have been advised on further treatments, including surgical measures where the condition seemed to indicate such interference.

TABLE III. *Cases Still on Refills*

Side.		Choice.			Fluid.	Larynx.			Sputum.		Totals.
L.	R.	I.	II.	III.		Healed.	Impd.	I.S.Q.	T.B. +	T.B. - or no sputum.	
13	15	14	13	1	13	4	—	—	7	21	28

There are twenty-eight cases now on refills for periods of one year to three years. Fluid has appeared in thirteen cases and has not interfered with the continuance of treatment. Twenty-one (75 per cent.) are now T.B. -. Phrenic evulsion has been performed in three cases, in two for threatened re-expansion, with definite success in that the treatment has been continued for eighteen months and two years respectively following the operation, and in one for threatened obliteration from the base upwards following hydropneumothorax, also with successful result. All four who had laryngeal tubercle are healed: one developed this complication while in the Sanatorium and under the treatment, but it healed with voice rest.

TABLE IV. *Cases Successfully Induced—Since Dead*

Side.		Choice.			Fluid.	Larynx.			Totals.
L.	R.	I.	II.	III.		Healed.	Impd.	I.S.Q.	
7	8	2	10	3	5	3	3	2	15

Fifteen cases in whom it was possible to induce treatment are since dead. It is worthy of note that ten of them died within a year of the induction of treatment, and of these ten, eight died of acute extension of disease to the other side, so that evidently pneumothorax was not efficient in arresting the progress of the disease. Apart from this cause of death, two died of pyopneumothorax, one of haemoptysis and one of complicating lymphadenoma. Seven were left-sided and eight right-sided cases, so that it is

impossible to draw any conclusion from these figures of the effect of pneumothorax on one side as against the other. Reference to Tables II and III will show that out of forty-two left-sided cases thirty-two (76 per cent.) are negative, while out of thirty-four right-sided cases twenty-eight (82.3 per cent.) are negative. The approximation of these percentages would tend to lead to the conclusion hinted at in the fifteen dead cases, that there is nothing to choose as between a left-sided and a right-sided case.

Out of ninety-one cases, a complicating hydropneumothorax has been found at some period during the treatment in forty-five, practically 50 per cent., but the fact that it appeared in twenty-seven of forty-eight cases (56.25 per cent.) that have now ceased refills and are still alive, probably gives a better idea of its incidence. Reference has already been made to the fact that it does not necessarily interfere with the continuance of the treatment, although reference to the tables and to the cause of death will show that it has gone on to pyopneumothorax in five cases, and has caused obliteration in ten.

TABLE V. *Unsuccessful Cases Still Alive*

Side.		Choice.		Sputum.		Cause of failure.	
L.	R.	II.	III.	T.B. +	T.B. — or no sputum	No space or small pocket.	Adhesions.
8	6	11	3	7	7	13	1

TABLE VI. *Unsuccessful Cases—Dead*

Side.		Choice.		Cause of failure.	
L.	R.	II.	III.	No space or small pocket.	Adhesions.
7	10	8	9	7	10

As previously noted, it was impossible to induce pneumothorax in thirty-one cases that seemed suitable for the treatment. Table V sets out in detail the statistics of the fourteen cases still alive. Three of them have a history up to two years, the other eleven are alive from three to seven years after the date of attempted induction. It is interesting to note that exactly 50 per cent. are negative, and that thirteen out of fourteen survivors were cases in which either no space or only a small pleural pocket was found.

It is also remarkable that exactly half are in good condition. One who is now negative has had a long course of Sanocrysin. Phrenic evulsion has been performed on four cases with good result, one has had upper thoracoplasty and is still in very poor condition. These results are to be compared with those set out in Table VI, which deals with the seventeen who are now dead. It is interesting to note that ten had to be given up because of gross adhesions, and it would seem from these two tables, V and VI, that while all cases in which pneumothorax fails should be pressed to go on to surgical treatment, it is particularly necessary to press for treatment in those where the treatment has been unsuccessful because of inefficient collapse of the lung through multiple adhesions that cannot be dealt with by cutting or cauterization. It is also worthy of note that seventeen of thirty-one failures

(54.8 per cent.) are dead; while only fifteen of ninety-one successful cases (16.5 per cent.) are dead.

Tables A and B set out all cases in detail from the points of view of immediate treatment and after-history. All cases were T.B. + before the induction or attempted induction of treatment, and the durations in those cases that are re-admissions are calculated from the date of admission prior to such treatment. The preceding tables give, of necessity, only a bird's-eye view of the situation, and they have marked limitations, most evident in Table I, and, to a less extent, in the others. These objections are that, first, all cases are not observed for the same period, but over periods ranging from one to seven years from the date of induction; and second, that they do not show the incidence of the deaths, although an after-history investigation in Table B shows that these objections are not so serious as would at first appear. No doubt, the ideal would be to deal separately with cases observed for 1, 2, 3, 4, 5, 6, and 7 years, but this would not be warranted in view of the limited numbers under review. An attempt has been made to overcome the first objection to a certain extent by giving in the after-history tables the average period for which cases in each Choice were observed.

Table A corresponds with Table J on page 22 of the Main After-History Report (1), and includes in addition columns showing the average number of weeks spent in the Sanatorium. These durations are comparable with the durations of treatment shown in Tables A-H (pp. 14-21).

The After-History Tables deal with five categories:—

Successful Cases—Choice I, Choice II, Choice III.

Unsuccessful Cases—Choice II, Choice III.

These give the same particulars as are given in Tables 2-15 (pp. 24-37) of the Main Report (1), but in view of the smaller numbers involved separation according to sex is not made, so that the expected deaths and, in consequence, the ratios of actual deaths to expected deaths, are approximate only. It is believed, however, that these are sufficiently accurate to give the general indications which are all that was hoped for in this investigation.

Choice III cases are observed, on an average, for $1\frac{1}{2}$ years from discharge, Choice I and Choice II cases for about $2\frac{3}{4}$ years. The fact that Choice III cases do not show better results in an appreciably shorter period of observation points to their unsuitability for this form of treatment. Deaths in Choice I and Choice II successful cases are concentrated in the first two years after discharge; the Choice III cases are too small in number to give any indication. In unsuccessful cases the deaths are spread over all durations. If the single death in the Sanatorium be taken into account, the percentages of deaths in various Choices are as follows:

	Successful	Unsuccessful
Choice I	5 per cent.	—
Choice II	22 „ „	39 per cent.
Choice III	42 „ „	57 „ „

These percentages, reflecting as they do the value of choice of case and the comparison of successful and unsuccessful treatments, are even more striking than the overall statement previously made, particularly in view of the shorter average period of observation in Choice III cases.

In considering these findings, admittedly based on small numbers, it is to be borne in mind that in all cases normal Sanatorium treatment had failed. They warrant the conclusion that pneumothorax treatment in Choice I cases gives results definitely superior to the general Midhurst results, which includes most of these cases. As regards Choice II cases, the results appear also to be better, except for the first two years after discharge, and this may be due in great part to the fact that the treatment was attempted generally in the more serious cases of the various sub-groups. Although the numbers of Choice III cases are too small for conclusions, they indicate quite clearly that the treatment at this stage can only be palliative at best.

Summary

This analysis of ninety-one successful and thirty-one unsuccessful cases of artificial pneumothorax gives clear indications on the value of the treatment in spite of the small numbers involved. It shows that a Choice I case has a better prognosis under artificial pneumothorax than a Group I case under ordinary Sanatorium routine, as shown by the recent Report on Mortality after Sanatorium Treatment (1); it warrants a similar conclusion on the average Choice II case, but does not encourage pneumothorax treatment in Choice III cases. The complicating hydropneumothorax may be expected in fully 50 per cent. of successful inductions, but it does not necessarily interfere with the normal length of treatment, nor need it unduly bias the prognosis. Pneumothorax would appear to be one of the quickest methods of curing laryngeal tuberculosis in cases otherwise suitable for such treatment. There is a better prognosis where no pneumothorax can be induced because no pleural space, or only a small pocket of air, is found at attempted induction, than in cases where it has been possible to start the treatment and later found necessary to abandon it owing to the presence of gross adhesions.

The writers would like to record their appreciation of the help given them by Miss F. M. Ackary, Record Clerk at King Edward VII Sanatorium.

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Unsuccessful cases

[illegible]

TABLE B. *Pneumothorax Investigation Men and Women*

Average age at discharge.	Dura- tion.	Exposed to risk.	Actual deaths.	Expected deaths.	Rates of actual to expected deaths.	Crude rate of mortality.	Corresponding crude rate in Midhurst general experience.
<i>Successful cases</i>							
<i>Choice I. 40 cases observed on the average for 2.63 years</i>							
29	0	37	1	0.15	6.7	0.027	0.043
	1	26	1	0.11	9.1	0.038	0.091
	2	21	—	0.09	—	0.000	0.105
	3	15	—	0.07	—	0.000	0.087
	4	7	—	0.03	—	0.000	0.078
	5	1	—	0.01	—	0.000	0.071
	6	—	—	—	—	—	—
		107	2	0.46	—	—	—
<i>Choice II. 45 cases observed on the average for 2.64 years</i>							
27	0	42	4	0.16	25.0	0.095	0.052
	1	33	5	0.13	38.5	0.152	0.114
	2	20	—	0.08	—	0.000	0.116
	3	15	—	0.07	—	0.000	0.097
	4	6	—	0.03	—	0.000	0.093
	5	3	1	0.01	100.0	0.333	0.070
	6	—	—	—	—	—	—
		119	10	0.48	—	—	—
<i>Choice III. 6 cases observed on the average for 1.33 years</i>							
26	0	6	2	0.02	100.0	0.333	0.138
	1	1	—	0.004	—	0.000	0.170
	2	1	1	0.004	250.0	0.000	0.202
	3	—	—	—	—	—	—
	4	—	—	—	—	—	—
	5	—	—	—	—	—	—
	6	—	—	—	—	—	—
		8	3	0.03	—	—	—
<i>Unsuccessful cases</i>							
<i>Choice I. Nil.</i>							
<i>Choice II. 18 cases observed on the average for 2.78 years</i>							
29	0	17	2	0.07	28.6	0.118	0.134
	1	12	2	0.05	40.0	0.167	0.195
	2	9	1	0.04	25.0	0.111	0.168
	3	7	2	0.03	66.7	0.286	0.160
	4	3	—	0.02	—	0.000	0.138
	5	2	—	0.01	—	0.000	0.078
	6	—	—	—	—	—	—
		50	7	0.22	—	—	—
<i>Choice III. 12 cases observed on the average for 1.50 years</i>							
32	0	12	7	0.06	116.7	0.583	0.334
	1	5	2	0.03	66.7	0.400	0.284
	2	1	—	0.01	—	0.000	0.293
	3	—	—	—	—	—	—
	4	—	—	—	—	—	—
	5	—	—	—	—	—	—
	6	—	—	—	—	—	—
		18	9	0.10	—	—	—

A CORRELATION OF CERTAIN BLOOD-DISEASES ON THE HYPOTHESIS OF BONE-MARROW DEFICIENCY OR HYPOPLASIA¹

BY F. GRAHAM LESCHER AND DOUGLAS HUBBLE

Introduction

A GROUP of blood disorders in which deficient production of the various elements formed by the bone-marrow may be demonstrated, and, although these cases are relatively few, they have importance out of all proportion to the rarity of their occurrence.

In one disease, aplastic anaemia, all the elements of the bone-marrow are deficiently produced; in another, agranulocytic angina, there is defective formation of granulocytes only; in the third, idiopathic purpura haemorrhagica, the platelets are greatly reduced. To this terminology, which is most commonly adopted, we shall adhere throughout this article, though at the end we suggest a nomenclature which co-ordinates these conditions. We have found in the literature three instances in which the erythrocyte production alone is deficient—pure red-cell anaemia. Many cases recorded in the literature are intermediate between these disorders, and in any theory of causation this must be accounted for. It is probably true to say that the dominating symptom will vary according to which element of the blood is most deficient. If the platelets are greatly reduced, haemorrhages and purpura result; if the most notable deficiency is in red-cell production, a severe degree of 'anaemia' shows itself, while if the granulocytes disappear from the circulating blood, infection is the most prominent clinical feature.

These diseases are of fundamental importance because they compel consideration of bone-marrow function and the factors which normally stimulate, control, and inhibit the production of the blood elements.

Agranulocytic Angina

Werner Schultz (1) was the first to describe this condition. Many other clinicians in Germany, France, and America have published further cases, but is a curious fact that while the haematological literature of these three

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countries contains more than a hundred cases, we have only been able to discover two case reports in the English literature, the first by Batten (2) and the second by Garrod and Williams (3).

This may be due to the fact that the disorder has not yet received such widespread recognition in this country, possibly because routine blood investigations are not so commonly employed. It is difficult to believe that it occurs here with less frequency, and a physician who searches his mind and his records will no doubt recall, as we do, cases in which agranulocytic angina suggests itself as the most probable diagnosis.

Clinical course. Agranulocytic angina occurs most typically in middle-aged women, and it has an acute onset with fever, ulcerative and necrotic stomatitis or pharyngitis, extreme granulopenia, and a clinical course which proceeds rapidly and without remission to a fatal end. This is Schultz's original description, and it still embraces the majority of recorded cases, but it is now recognized that the incidence, symptomatology, and the clinical course may show wide variations. Thirty per cent. of recorded cases have occurred in males (4, 5), while no age is exempt. Roberts and Kracke (6) describe a case in an old lady of 72, while Rutledge and others (7) report it in a young man of 19 in whom the condition had been present since infancy.

The two essential features of the disease are the presence of sepsis and a typical blood picture. It is significant that the sepsis occurs in those regions of the body which contain the greatest number of potentially pathogenic organisms, i.e. the mouth, pharynx, rectum (8), the vagina, and the skin (9). Consequently, a bewildering array of organisms has been advanced as a 'cause' of the disease in spite of the fact that blood cultures are usually sterile. Most typically the mouth and pharynx is covered by a membrane, whiter and less tough than the membrane of diphtheria, which may be removed without haemorrhage.

The blood changes are highly characteristic. The red cells, the haemoglobin, and the platelets are generally within normal limits, but there is a reduction in the total leucocyte count, which is due to a rapidly progressive diminution in the granular leucocytes, neutrophils and eosinophils, from the blood.

The total leucocyte count may fall as low as 100 per c.mm., and is always below 2,000 per c.mm. in fatal cases. It follows from this that any lymphocytosis is only apparent, and that there is invariably a reduction of lymphocytes. It is often impossible to find a granulocyte, though an occasional myelocyte or myeloblast may be seen after careful searching (10).

The other clinical signs are of less importance. The onset is usually abrupt, and occurs in persons of good health. There is fever, malaise, and general prostration. Jaundice is described in about half the cases (4), and this is probably due to a hepatitis (the liver is sometimes described as enlarged and tender), as there is no evidence of any haemolysis. The spleen is sometimes enlarged. Two negative clinical points of importance in differential diagnosis are the absence of any marked enlargement of

lymphatic glands, including the cervical glands, and the absence of haemorrhages and purpura (11).

The duration of the disease is usually short, varying from four to eight days, and death is frequently preceded by a terminal broncho-pneumonia (5).

The disease is usually fatal, although there are now several cases of recovery recorded, and in the majority of cases in which recovery takes place the blood picture returns to normal limits, but Rosenthal (12) has reported a case in which a granulopenia persisted after recovery. Several cases of recovery with subsequent relapse have been published, and sometimes death has occurred in the second attack (6, 13), but many attacks in the same patient have been noted (14).

A most remarkable and indeed unique case has been recorded by Rutledge, Hansen-Prüss, and Thayer (7). The patient, a young man, has had recurrent attacks of agranulocytosis, with fever, malaise, and necrotic lesions in the pharynx, which have been observed since infancy. The attacks varied in severity and lasted from six to ten days; they were preceded by a marked decline in the polymorphonuclear leucocytes in the blood. The attacks occurred with more or less regular frequency, the average cycle being of three weeks' duration, and in between them he was in good health and his granulocytic count was normal. This case is referred to again below.

Pathology. The bone-marrow at autopsy appears normal, but microscopically there is marked diminution or total disappearance of the granulocytes and myelocytes. In some of the recorded autopsies the marrow is described as 'fatty', and these cases must be considered as intermediate between agranulocytic angina and aplastic anaemia. If death occurs after regeneration of the granular cells has begun, the marrow may show evidence of acute haemopoiesis with cells normal in number and character. There may even be evidence of myeloid hyperplasia (6). Kastlin says, 'associated with the disappearance of granular cells from the bone-marrow and circulating blood, the reticulo-endothelial cells are increased at their sites of formation and in the circulating blood. Histologically, these cells are seen to be phagocytic, and I believe, in the absence of granular cells, they remain as the chief cellular combatants to infection' (5).

A notable pathological finding is the lack of any normal inflammatory reaction. A microscopical examination of the necrotic areas does not show the usual zone of polymorphonuclear cells. Similarly, no granulocytes are seen in the spleen; and the histological picture of septic splenitis is never present. There is no evidence *post mortem* of focal sepsis.

Differential diagnosis. We do not propose to discuss differential diagnosis in detail. Gordon and Litvak report an interesting series of eight cases admitted to an isolation hospital as diphtheria. The final diagnosis was agranulocytic angina in four cases, two cases of acute lymphatic leukaemia, and one each of leukaemia in an aleukaemic phase and myelogenous leukaemia (15).

Blumer has pointed out (16) that the differential diagnosis between aleukaemic leukaemia and agranulocytic angina is sometimes impossible until the case comes to autopsy.

Poisoning by benzol and X-rays, &c., may result in an agranulocytic blood picture with characteristic sequelae (*vide infra*).

Some cases of agranulocytosis show profound anaemia, and others haemorrhages with thrombopenia: there is no clear distinction on the one hand from aplastic anaemia and, on the other, from idiopathic purpura haemorrhagica.

We discuss below reports of agranulocytosis in which the granulopenia undoubtedly develops secondarily to some septic condition. Kastlin believes that these cases can be distinguished from idiopathic agranulocytic angina, usually during their clinical course and always at autopsy (5).

Aetiology. It is now well established that the agranulocytosis is due to deficient production of granulocytes in the bone-marrow and not to their excessive destruction in the circulation. This is suggested by the histological appearance of the bone-marrow at autopsy. Further proof was obtained by the removal of bone-marrow during life in three cases. Microscopical examination showed a 'a cell-poor marrow with decrease in the granulocytic elements the same as was seen at necropsy. The hypoplasia of these granular cells is thus not a terminal event, and the decrease of the cells in the blood-stream appears to be due to the failure of development of the cells in the bone-marrow' (4).

It is also established that the necrotic lesions are secondary to the depression of the granulopoietic function of the marrow. It has been shown in several cases that the blood changes occurred before the ulcerative stomatitis developed (7, 17). The best demonstration of this fact was given by Roberts and Kracke (6) in a case of exceptional interest. This patient was a lady of 72, whose blood was examined daily for 2½ months. She had recovered from a typical attack of agranulocytosis and her leucocyte count had returned to normal; but, after a month's further observation, the neutrophils again commenced to disappear from the blood, and in three days they were entirely absent; 'but the patient was as well as usual, actually dancing a few steps to show us how well she was. We looked on in amazement, waiting for the clinical storm to break.' Next day the typical agranulocytic attack developed, and in four days she was dead.

The occurrence of similar necrotic lesions in acute lymphatic leukaemia and in aplastic anaemia affords further corroborative evidence that the lesions are secondary to the granulopenia. There is, however, no agreement as to the cause of the deficient granulopoiesis.

Some authors maintain that agranulocytosis is not a clinical entity but a syndrome of the same sort as 'anaemia, monocytosis, or eosinophilia' (11, 18). Others, such as Kastlin, are more precise and regard agranulocytic angina 'as a particular biologic type of haemopoietic reaction to infection. This reaction may be influenced, as Türk has stated, by the

type and strength of infection on the one hand and by the individual reaction to infection' (5).

Rosenthal, on the contrary, is of the opinion that 'the leucopenia is possibly due primarily to a functional disturbance or a hypoplasia of the leucopoietic system' (12), and Zikowsky relates the deficiency of the leucopoietic function of the marrow to a 'severe attack on the organs whose duty it is to excite the activity of the marrow, most possibly the endocrine system—liver, spleen, and certain glands' (19).

A study of the recorded cases suggests that both these opposing views may be correct. In the pure, idiopathic type of a granulocytic angina the sepsis appears to be secondary to the granulopenia, and there is no evidence, during life or at autopsy, of any infective agent. The case of recurrent, cyclic agranulocytosis reported by Rutledge and others (7) suggests a functional hypoplasia of the leucopoietic system, and this would seem the most reasonable explanation of the idiopathic cases. There is no doubt, however, that sepsis may depress leucopoiesis so that the haematological and clinical picture of agranulocytic angina develops.

Several infections, such as enteric, rubeola, and varicella, are well known to produce a granulopenia; and it is not rare for severe septicaemic states to depress granulopoiesis still further. Smith (20) reports a case of lateral sinus thrombosis in which the polymorphonuclear cells numbered 60 per c.mm. in a total leucocyte count of 1,900 per c.mm.

Türk (21) was the first to describe severe septic conditions which show an extreme neutrophilic leucopenia and relative lymphocytosis. Clinically, the course of the disease is similar to agranulocytic angina, but they show, in addition to gangrenous stomatitis, the haemorrhagic diathesis with marked anaemia and thrombopenia. Kastlin (5) points out that these cases are differentiated, too, from idiopathic agranulocytic angina by the invariable presence of septic foci, positive blood cultures, and, at autopsy, the septic type of splenitis.

It seems probable to us that the cases just referred to result from excessive destruction of granulocytes in the circulating blood; unfortunately, the distinction between deficient production and excessive destruction of granulocytes is not clinically easy, as it is in the case of the erythrocytes. Even if these cases are separated from true agranulocytic angina there still remain some in which 'infectious lesions are present before the onset of acute disease and then have shown a progressive decrease in granular cells as the disease progressed, suggesting the infection as the cause of the bone-marrow depression by toxic action' (5).

Chevallier (11) quotes two cases in which there was prodromal jaundice, and the blood examination was, at this stage, found to be normal, and with the progress of the disease agranulocytosis developed.

It is reasonable to conclude, therefore, that while in some cases the depression of granulopoiesis is due to some infective agent, yet in typical idiopathic agranulocytic angina it is more likely that a hypoplasia of the

granulopoietic system is present. We discuss treatment below in conjunction with aplastic anaemia and purpura haemorrhagica.

Idiopathic Purpura Haemorrhagica

There has been much discussion concerning this syndrome, and it must be admitted that the facts, both clinical and experimental, are so confusing that the dogmatic enunciation of any theory is unwarranted. A few years ago it was generally accepted that there were certain clinical and pathological characteristics which distinguished one group of purpuras from all others, and this group has been variously named idiopathic purpura haemorrhagica, Werlhof's disease, essential thrombopenia (22), and thrombocytolytic purpura (23, 24). It was believed that in this disorder, unlike other purpuras, there was a great diminution in the circulating blood-platelets, that this platelet deficiency was responsible for the purpura and capillary haemorrhages, and, although no cause was known, splenectomy was thought to be a permanent cure. All these statements have, of recent years, been denied by many observers, and discussion has centred round the four following points: (1) Can idiopathic purpura haemorrhagica be separated from other purpuras? (2) Is the platelet deficiency due to their over-destruction or their under-production? (3) Is the reduction in platelets primarily responsible for the capillary haemorrhages? (4) Is the disease caused by excessive splenic function? A brief review of the discussion of these questions is given below, but idiopathic purpura haemorrhagica may still be considered an entity (although like many other blood disorders its borders are often ill defined), that the platelet deficiency is concerned in the production of the capillary haemorrhages, and that the platelets are deficiently produced by the bone-marrow. Therefore, although many observers would not consider it justifiable, idiopathic purpura haemorrhagica is included by us in the group of blood disorders in which there is deficient production of the blood elements by the bone-marrow, i.e. aplastic anaemia and agranulocytosis. To do this is to insist that, aetiologically, all cases of purpura haemorrhagica are strictly in line with these other haemopoietic disorders. As is pointed out below, the facts suggest that, eventually, purpura haemorrhagica itself will be divided into at least two groups—one in which there is deficient production of megakaryocytes by the bone-marrow—another in which there is defective separation of the platelets from the megakaryocyte, possibly due to deranged splenic function. The first group will be allied to aplastic anaemia, and the second may very well be linked up with splenic anaemia.

(1) *Can idiopathic purpura haemorrhagica be separated from other purpuras?* It is still impossible to make a satisfactory aetiological grouping of the purpuras, and it is preferable to adhere to the following clinical classification:

(a) *Symptomatic purpura.* Purpura may be a symptom of a large number

of diseases, including infective, toxic, cachectic conditions, and certain blood-diseases such as pernicious anaemia and lymphatic leukaemia. In many of these disorders the purpura is attributed to a capillary defect; in others, especially in the toxic conditions and blood-diseases, it may be accompanied by a thrombocytopenia.

(b) *Anaphylactoid purpura* (Henoch-Schönlein). Most observers are agreed that this is a well defined group. The skin lesions in this group are distinctive—the purpura is often accompanied by urticaria or by erythema exudativum, and occasionally by vesication. There is very seldom haemorrhage from mucous membranes in this group, and the blood-platelets are present in normal numbers. The two most prominent symptoms are articular pains (Schönlein) or gastro-intestinal crises (Henoch).

Tidy (25) has recently pointed out that nearly all cases of purpura of more than the slightest severity have joint pains. This is true of this group and purpura simplex, but it is extremely rare in the literature to read of articular pain occurring in purpura haemorrhagica.

(c) *Purpura simplex*. This is a mild form, occurring most commonly in children. There is often articular pain, and some clinicians have classed it with the previous group, but as the characteristic skin lesions are absent it is perhaps better to differentiate it. The patient gets well in less than a fortnight, and it is distinguished from purpura haemorrhagica by its short course, non-intermittent and non-remittent, the absence of haemorrhages from mucous membranes, and the normal platelet count (*vide infra*).

(d) *Purpura haemorrhagica*. In the last few years many cases have been recorded by Roskam (26), Mackay (27), Poinso and Jouglaard (28), and others which have all the clinical characteristics of purpura haemorrhagica, but in which the platelet count is always within normal limits. Frank (29), Kaznelson (30), and Rosenthal (31) have explained these cases, now well established, by postulating that the platelets, though normal in numbers, are deficient in function. As Mackay has pointed out, there is very little evidence of this, and, indeed, it is not an hypothesis very susceptible of proof, since the function of the platelets is as yet unsettled.

Although thrombocytopenia is not invariably present in purpura haemorrhagica there is general agreement among clinicians (with a few exceptions (25)) that this disorder may still be differentiated from other purpuras and that a deficiency in platelets is its most important clinical sign. A description of its main clinical features is given at the end of this section.

(2) *Is there under-production or over-destruction of platelets?* Frank (22), in 1915, suggested that there was in purpura haemorrhagica (essential thrombopenia) a deficient production of platelets by the bone-marrow, while Kaznelson (23, 24) later maintained that there was normal production of platelets, but that they were excessively destroyed by the spleen (thrombocytolytic purpura). He gave a bold demonstration of the truth of his theory by causing splenectomy to be done for the first time in the treatment of the condition. Frank explained the success of the operation

by the hypothesis that the spleen inhibited the production of platelets. The clinical and pathological evidence supporting an excessive destruction of platelets by the spleen is not good, and both Piney and MacKay, after reviewing it in detail, conclude that the more probable view is that there is interference with the normal production of platelets by the bone-marrow.

Tidy (25) is of the opinion that the platelet reduction is secondary to the haemorrhages, and as his views have received some acceptance in the English literature, they are critically reviewed here. He believes that the following factors bring about a reduction in platelets: (a) *The haemorrhages may lead to aplasia or anaplasia of the bone-marrow.* It is shown below, when the pathogenesis of aplastic anaemia is considered, that there is little evidence which suggests that haemorrhages, even large and repeated, result in aplasia of the marrow or a true aplastic blood picture. Where evidence of aplasia of the marrow exists it is to be regarded as a primary phenomenon. (b) *Defective platelets are produced in large numbers and destroyed by the spleen.* It is true that there are morphological characters, such as basophile staining, in the platelets in purpura haemorrhagica which suggest immaturity, but of the excessive destruction of these immature platelets by the spleen there is no direct evidence.

An attempt has been made to get direct evidence of platelet destruction in the spleen by comparative platelet counts in the blood of the splenic artery and vein. Holloway and Blackford (32) were unable on repeated occasions by this method to detect any marked difference in the platelet counts in normal animals; other observers have reported varying results in man. Krumbhaar (33) states that these comparative blood counts are particularly unreliable, and even if there were proved to be a notable discrepancy between the number of platelets in the splenic artery and vein, it would still be necessary to take into account the reservoir action of the spleen. (c) *The platelets are withdrawn or consumed in their attempts to check the haemorrhages.* If this were true the platelet count should vary inversely with the number and severity of the haemorrhages, and of this there is no indication. Again, as MacKay has pointed out, there is no great diminution of platelets in these conditions in which there is damage to or alteration in the permeability of the capillaries, such as scurvy or Hænoch's purpura.

There is then little evidence which supports this view of platelet reduction, and in spite of the admitted difficulties, the theory that there is deficient production of platelets by the bone-marrow is more acceptable.

(3) *Is the platelet reduction responsible for the haemorrhages and purpura?* Bedson's (34) experiments have shown that a platelet reduction alone is not sufficient to cause purpura in animals, and that the necessary added factor is damage to the endothelium of the capillaries. The clinical facts that extreme thrombocytopenia may sometimes be present in the absence of spontaneous capillary haemorrhages, and prolongation of the bleeding-time may exist while platelets are present in normal and increased numbers, have led many observers to maintain that the platelet deficiency has no

part in initiating the capillary haemorrhages. They conclude, therefore, that the haemorrhages of purpura haemorrhagica are due to defect in the capillary walls—angéioses parcellaires hémorragiques (Roskam). Even Roskam, a strong supporter of this theory, admits that the platelet-deficiency will increase the severity of the haemorrhages (35).

MacKay has recently summarized the evidence against the theory that the thrombocytopenia is a primary cause of the haemorrhages (27) and he regards it as a secondary phenomenon, the result of deficient production by the bone-marrow due possibly to 'some metabolic disturbance or to deficiency of some internal secretion'.

Although it is impossible to be as dogmatic as Kaznelson (30) who maintains that 'there is no Werlhof's disease without thrombocytopenia', yet the supporters of the theory of capillary defect appear to underestimate the almost complete constancy with which thrombocytopenia is associated with capillary haemorrhage and purpura. They give little consideration to such blood disorders as aplastic anaemia, in which there is simply a bone-marrow deficiency with diminished production of the blood elements, and no suggestion of capillary affection. In cases of aplastic anaemia in which there is no great reduction of circulating platelets, haemorrhages and purpura do not occur. This is shown in cases quoted by Strain (36), by Lupu and Nicolau (37), and in the first of our series of four cases (38), in which the platelets numbered about 70,000 per c.mm., for several months without any purpuric eruption; but on one occasion when a large crop of purpuric spots appeared the platelets were 20,000 per c.mm. However, the relative importance and the possible inter-action of platelet and capillary in the production of haemorrhages is not finally settled. As Askanazy (39) remarks 'les malades souffrant de thrombopénie manifestent la tendance à faire des hémorragies multiples, ce qui paraît indiquer la fonction des plaquettes de garantir l'état colloïdal normal des endothéliums vasculaires dont la perméabilité augmente avec la pénurie des plaquettes. . . . L'avenir montrera ce qui va rester de ces idées encore hypothétiques'.

(4) *Is the disease caused by excessive splenic function?* The possibility of an endocrine action of the spleen on haemopoiesis makes it difficult to interpret laboratory experiments and clinical evidence as to the role of the spleen in the causation of purpura; results which may equally well be attributed to an inhibitory action of the spleen or blood formation are attributed to destruction of the circulating elements by the spleen. Especially is this so in purpura haemorrhagica, for with the platelets, unlike the red cells, it is impossible to get reliable evidence of their excessive destruction.

Bedson (40) found that after splenectomy in guinea-pigs the platelet count was doubled after two or three days, but it had fallen again to normal after thirty days. These observations showed, he assumed, that in this time the rest of the reticulo-endothelial system had taken over the destruction of platelets, which normally went on in the spleen.

It is interesting to remember, that in those cases of splenic anaemia in

which there was a thrombocytopenia, Howel Evans (41) recorded after splenectomy a similar platelet curve to that obtained by Bedson in his experiments on guinea-pigs, with these differences, (1) that it was ninety days before the count returned to normal figures, and (2) that the count did not return to its previous figure, but remained within normal limits. These observations suggest that there must therefore have been two factors at work, (1) the normal destruction of platelets by the spleen, which was in three months taken over by the reticulo-endothelial system, and (2) an added inhibitory factor on platelet-formation, which was removed permanently with the spleen.

The results of splenectomy in purpura haemorrhagica are not by any means so constant, and Piney (42) has divided them into three groups: (a) In which there is a rapid and persistent rise in the platelet count to normal (or above normal) figures. There is invariably clinical cure in this group. (b) In which there is a rise after operation, but within a short time the platelets again fall to a low figure. There is usually clinical cure, but sometimes there is, in the late history, a recurrence of mild or severe haemorrhages. (c) In which there is practically no change in the platelet count, although there was a marked thrombocytopenia before operation. There is often clinical improvement. If there is a good clinical result without a corresponding rise in platelets after splenectomy, it has been attributed by supporters of the platelet theory to the improved quality of the platelets; though most observers maintain that there is little morphological evidence of this.

To these might be added a fourth group in which the platelets fall, sometimes considerably, after operation. Both Bond (43) and Findlay (44) have recently described cases of this type. It is obvious, therefore, that the spleen must be exercising a differing effect on the platelets in these groups. In the first group, either the spleen is excessively destroying platelets or inhibiting their formation; in the second, it may be simply carrying out its normal destructive function; in the third and fourth groups, it is impossible to account for the persistent thrombocytopenia, especially when it is accompanied by marked clinical improvement as it is in some cases (26). Much of the difficulty, both in the theories of pathogenesis and in the interpretation of these therapeutic results, occurs, in all probability, because there are two or more types of purpura haemorrhagica as yet impossible to differentiate.

There is other evidence which suggests that purpura haemorrhagica will eventually be subdivided into groups. It is generally accepted that the platelet is derived from the megakaryocyte, and Minot (45) has observed a normal or excessive number of megakaryocytes in the bone-marrow in some cases of thrombocytopenic purpura. Askanazy (39) agrees, but maintains that these megakaryocytes are definitely abnormal in morphological characters. Both observers also define another group in which megakaryocytes are greatly reduced in the bone-marrow.

These facts, with the varying results of splenectomy, make it possible that the thrombopenic purpuras may eventually be divided into two or more groups. (1) In which there is deficient production of megakaryocytes. (2) In which there is defective separation of the platelets from the megakaryocyte. With possibly a third group in which there is excessive destruction of platelets by the spleen, though it is probable that when excessive splenic function plays a part, it is by an inhibitory action which is productive of either the first or the second type.

We conclude then from this survey that it is still worth while to define a group of purpuras, which the great majority of clinicians is agreed has the following characteristics: Most often the disease occurs, or commences, in children or young adults, and it may be acute or insidious in its onset. The disease runs commonly an intermittent course. Cases which are congenital and familial undoubtedly exist, though they are often confused with haemophilia. Usually there is no evidence of infection or sepsis, and the onset is usually abrupt, with bleeding from one or more mucous membranes, and with a purpuric eruption. The spots are always haemorrhagic, and may vary in size from minute petechial to large haemorrhages several inches in diameter. The spleen is only enlarged in the chronic and recurrent cases, and it seldom reaches a great size. The blood, in addition to the marked thrombopenia, may give a picture of post-haemorrhagic anaemia with evidence of increased erythropoiesis.

Tidy (25) has drawn attention to the cases in which there is evidence of some degree of aplasia of the bone-marrow, and points out that cases have been recorded in which there is a relative lymphocytosis, and the neutrophils are almost entirely absent. These are very important, and are to be regarded as intermediate between purpura haemorrhagica and agranulocytic angina. There is good evidence of the primary involvement of the bone-marrow and they are referred to again below in the section on treatment.

However, the great majority of cases show a leucocytosis. The coagulation time is normal according to most observers. Minot (45) for example, found that with a marked thrombocytopenia, the coagulation time is normal, or only slightly delayed. Cramer and Bannerman (46), however, disagree, and believe that it is always delayed; they criticize the method and care exercised in the reported cases, and maintain that if the conditions are rigidly standardized a delay of thirty seconds is significant. Howel Evans's (41) results are in agreement with this, and it appears probable that although these observers are at present in a minority, they may ultimately prove to be correct.

The bleeding-time should be definitely and greatly prolonged, and non-retractility of the clot can usually be demonstrated. The capillary-resistance test is, as MacKay (27) points out, not of diagnostic importance, as it may be elicited in other diseases, and is not invariably present in purpura haemorrhagica, but it seems certain that a profuse crop of spots of fair size (from 1 mm. to 1 cm.) only occurs in this disorder.

The course of the disease varies greatly. Death may take place in the first attack (a case of purpura fulminans which we have lately seen, died in the first attack within twenty-four hours from the onset) or after many months or years. There may occasionally be no second attack, although the disease runs a course that is remittent or intermittent. The remission may last a few weeks or many years. During the remission the platelets are typically below the normal average, but in some of the chronic cases the platelet count remains in the danger zone, and slight bleeding is persistent.

Differential diagnosis has to be made from all other types of purpura, and chiefly from the two main groups: (a) the thrombopenic purpuras which are symptomatic, i.e. occurring in severe intoxications or infections, anaphylaxis, the leukaemias, and pernicious anaemia. (b) the group of non-thrombopenic purpuras. In this article the main concern is with the differential diagnosis from aplastic anaemia, and this distinction can usually be made. Many cases in the literature as Minot (47) says, are 'intermediate between idiopathic aplastic anaemia with symptomatic purpura haemorrhagica and idiopathic purpura haemorrhagica. From such cases it is suggested that these two conditions may, perhaps, be not distantly related, for one can find cases of these idiopathic conditions, where the blood picture can be interpreted as showing all degrees of involvement of the three chief elements of the marrow.' In well-defined cases the differential diagnosis depends on the following points. The haemorrhages occur in idiopathic purpura haemorrhagica before the anaemia is obvious, whereas, in aplastic anaemia, the anaemia is usually apparent before there is purpura. In both conditions there is a thrombocytopenia, but in aplastic anaemia there is no evidence of red and white cell regeneration, while in purpura haemorrhagica after haemorrhage, there are numerous immature red and white cells in the blood. *Post mortem* the marrow, at least in aplastic anaemia, is distinctive. The second of our cases of aplastic anaemia (38) and a case described by Spence (48) (referred to below in the section on treatment) illustrate very well these points in differential diagnosis.

Pure Red-cell Anaemia

The first example of this type was recorded by Kaznelson (49) in 1922. It developed in a man aged 58 in the course of three weeks. A characteristic blood count was: erythrocytes 552,000 per c.mm., haemoglobin 12 per cent.; colour index 1.07; leucocytes 4,980 per c.mm., in normal proportions; blood-platelets 207,000 per c.mm. There was no sign of regeneration of the erythrocytes. Sections of the red-marrow at autopsy showed no nucleated red cells, but a moderate cell content containing only neutrophils, eosinophils, myelocytes, and megakaryocytes. Baar (50) described the second case in 1927 in a girl aged 3 years. A typical blood count was:

haemoglobin 13 per cent.; red corpuscles 800,000 per c.mm., leucocytes 2,200 per c.mm., platelets 180,000. There was no sign of erythropoiesis in the blood, but there was evidence of active leucopoiesis. The post-mortem appearance of the bone-marrow was similar to that in Kaznelson's case. All the formed elements were present in normal numbers, except the red cell and its precursors. It is to be noted, however, in Baar's case that the anaemia followed upon a disorder diagnosed as influenza and, as in the count quoted above, there was a definite leucopenia. This suggests the possibility that the original infection may have followed on a granulopenia from which the bone-marrow was recovering, but death occurred before the production of leucocytes returned to normal.

Lupu and Nicolau (37) quote a third and similar case recorded by Brenn in which there was a destruction of the erythropoietic system, and called by him 'l'érythrophthisie post-infectieuse progressive'.

Although of great rarity, these three cases are of exceptional interest, when an attempt is made to co-ordinate the aplasias of the bone-marrow.

Aplastic Anaemia

Aplastic anaemia, first described by Ehrlich (51) in 1888, is a name given to a condition, in which there is a progressive diminution in the formation of those elements of the blood, the erythrocytes, granulocytes, and blood-platelets, which develop in the bone-marrow. They are not produced in sufficient numbers to compensate for the natural destruction, which is always taking place in the reticulo-endothelial system.

Causation. In most instances of aplastic anaemia the cause is unknown—the so-called idiopathic type, with which we are concerned particularly in this paper. But there are some cases, which may be secondary to the following known causes.

(a) *Benzol* and its derivatives. The action of this chemical on the bone-marrow is often selective, the platelets and granulocytes tending to be attacked first, and their production to be inhibited, thus giving rise to symptoms of purpura haemorrhagica, and agranulocytosis. Recovery may take place at this stage, or the attack may advance, the final objective being the erythroblastic tissue, a condition of aplastic anaemia thus resulting. Many cases have been reported in the literature, such as those by Bamforth and Elkington (52), Selling (53), Larrabee (54), and others. Selling injected benzol into rabbits, causing a thrombopenia with symptoms of purpura haemorrhagica. It was only by increasing the dose, and extending the time, that the granulocytes were attacked, and only in one case was a profound anaemia produced. Examination after death showed aplasia of the bone-marrow. Selling gives an account of three patients, who had worked in a canning factory with benzol. Two suffered from purpura haemorrhagica with necrosis of the tonsils, and later aplastic

anaemia supervened. Both died, and the marrow of the femora showed aplasia. In the third case, which was slight, a purpuric eruption was the only sign, being accompanied by diminution of the platelets; the granulocytes and erythrocytes were not involved. In Larrabee's case the march of events was a little different. It was one of benzol poisoning, in which the granulocytes were first attacked, the patient suffering with an acute infection of the pharynx with a marked diminution of these cells. Symptoms of purpura haemorrhagica followed with a thrombopenia; and lastly, the erythrocytes were involved as well. An autopsy showed an aplastic bone-marrow. Bamforth and Elkington have reported four cases of 'arseno-benzol purpura' in syphilitics, after prolonged treatment with an arseno-benzol compound. In two cases the platelets only were diminished in quantity. There was no leucopenia or anaemia; the chief symptoms being bleeding from the gums, with petechiae and ecchymoses on the extremities. After treatment with blood transfusion, liver powder, and sodium thio-sulphate, both recovered. In the other two cases the attack started with diminution of the platelets, but later affected the granulocytes and erythrocytes, giving a picture at first of purpura haemorrhagica, and later of aplastic anaemia. Both died, and an autopsy showed the marrow of the femora to be fatty (in one case there were a few areas of hyperplasia), with very few nucleated and non-nucleated erythrocytes.

(b) *Mustard gas.* During the Great War poisoning by mustard gas occasionally produced a depression in the production of bone-marrow cells. The formation of granulocytes and thrombocytes was first attacked, and later that of the erythrocytes. Sometimes by a great effort on the part of the bone-marrow the number of red cells was raised by the pouring in of immature forms; in other cases death took place, and the marrow was found to be aplastic. Krumbhaar (55) quotes a typical example of this.

(c) *Excessive exposure to irradiation.* (X-rays and radium.) Rolleston (56) in a critical review of the harmful effects of irradiation on the blood and blood-forming organs, has reviewed the literature of the subject, and arrived at certain conclusions.

The effects of irradiation may be twofold, depending on the strength of the rays, the length of exposure, and the susceptibility of the individual. With small doses of 'soft' radiations, a stimulating effect may take place, as shown by some increase in the number of lymphocytes, granulocytes, blood-platelets, and red cells. An attempt is made to obtain this result, by treating such diseases as aplastic anaemia, and agranulocytic angina by irradiating the long bones. But stronger doses of radiation may have an inhibitory effect, shown at first by a reduction of the lymphocytes, as they are the most radio-sensitive cells to the rays. Later the bone-marrow elements are likely to become affected, with a diminution first of the granular cells, so that there may be a relative lymphocytosis, and later a reduction of the erythrocytes, and a thrombopenia. As to whether the damage is done by action of the radiation on the cells, or on the haemo-

poietic tissue, most observers consider it to be on the latter, and this would bring it into line with other haemopoietic poisons, e.g. the action of benzol on the bone-marrow. If the damage to the bone-marrow is severe, then aplastic anaemia should develop. A number of cases have been reported by different observers, and have been collected by Rolleston (56). This disease has occurred among workers with X-rays and radium, and also among sufferers from diseases such as leukaemia, who have been treated by radiation. The gamma rays of radium are considered to reach the bone-marrow more readily than X-rays do, and are thus more likely to cause aplastic anaemia. Hoffman (57) and Flynn (58) have given an account of an outbreak which occurred at Orange, New Jersey, among workers employed in painting dials of instruments with luminous paint, containing small amounts of radium and mesothorium. They pointed the paint brushes with their lips, thus ingesting radio-active substance. A rapid necrosis of the jaw resulted, accompanied by severe anaemia of the aplastic variety.

(d) *Sepsis*. It is said that such infective conditions as overwhelming sepsis, malignant endocarditis, miliary tuberculosis, typhoid, diphtheria, can cause aplastic anaemia. This is discussed later.

(e) *Parasites*. Anaemia, either of the simple or, more rarely, of the megalocytic type, follows the infestation of such parasites as the ankylostoma and the bothriocephalus. Faberi (59), however, has reported the case of a child aged 6 years with a blood count of the aplastic type. Ova of *Trichocephalus dispar* were found in the stools, and the anaemia was partly attributed to this. The child was remarkably improved by irradiation of the femur, spleen, and tibia.

(f) *Exhaustion of the bone-marrow*. Partial or total aplasia sometimes occur in pernicious and other anaemias, such as haemolytic anaemia, especially as a terminal event when the marrow is becoming exhausted. Witts (61) says that a thorough examination of the marrow in pernicious anaemia always reveals some areas of complete aplasia, though in the majority of the bones the marrow is hyperplastic. The reaction of the bone-marrow in certain diseases with gastro-intestinal lesions such as sprue, fatty, and chylous diarrhoea, coeliac disease, and pellagra may be megaloblastic. Later the marrow can become exhausted when a blood picture of aplastic anaemia results. Fairley, Mackie, and Billimoria (65) have examined the bone-marrow of eight cases of sprue; in three there was megoblastic degeneration, and in five aplasia.

(g) *Other causes*. Aplastic anaemia may follow tumours of the bone-marrow and osteosclerosis by crowding out the myeloid tissue, a condition termed by some myelophthisis. In leukaemia, both lymphocytic and myelocytic, a similar result may take place.

Clinical course. Aplastic anaemia occurs most commonly in people from 15 to 30 years of age, though a small number of cases have been reported in children, and older people are not exempt. Females are said to be more frequently attacked than males.

The onset is insidious, the symptoms being a progressive loss of strength and energy, with breathlessness and increasing pallor. Occasionally there is a story of the patient not having been strong since birth, but more often the past history is one of good health. In a well-established case beyond pallor, the results of examination are largely negative. There is no undue loss of weight, no enlargement of the liver, spleen, or lymphatic glands. Glossitis and abnormal signs in the central nervous system are absent. No signs of blood destruction such as excess of urobilin in the urine and jaundice are present. Achlorhydria is said to be absent. There is often some fever, generally associated with sepsis in some part of the body, usually in the pharynx. Haemorrhage into the skin, or retinae, from mucous membranes, and in fact into any organ can occur, but this is relatively late in aplastic anaemia. The heart is generally dilated, and a systolic murmur is often present.

The blood picture. In a well-marked case the red cells fall to below a million per c.mm., with a corresponding reduction in haemoglobin. The erythrocytes are well filled with haemoglobin, and are of normal size and shape; the colour index being generally at or below unity. These cells stain evenly, and it is but rarely that an immature one is found. The number of reticulocytes is usually not raised, though in Witts's case the percentage rose to 6 per cent. on one occasion. This indicates the loss of power of regeneration by the bone-marrow and is one of the distinctive features of the blood examination of this disease. So much so that Dyke (66) has said that the detection of even a single embryonic red cell in a blood film is sufficient to exclude a diagnosis of aplastic anaemia. Yet there are exceptions, for Cabot (67) has reported a case of a man suffering from this disease, from whom a blood film gave evidence of marked signs of attempted red-cell regeneration. An autopsy showed aplasia of the bone-marrow. The second one of our series of cases (38) showed this, and it is perhaps to be expected, for it is rare to find even in this condition a completely aplastic bone-marrow.

Minot (45) says that the fragility of the erythrocytes is abnormal, the cells commencing to break up in about the normal strength of salt solution, but complete haemolysis occurs in a stronger solution than normal. In only one of the cases of our series (38) was the fragility of the red blood-cells tested, and it proved to be normal against a control.

Since in aplastic anaemia all the myeloid elements in the marrow are involved, the number of leucocytes is diminished and the relative proportion of the polymorphonuclear and eosinophile cells are decreased in number, and may even be absent. It is for this reason that infections are so common in this disease. There is a relative, but not an actual, lymphocytosis of the small cell variety, the percentage not usually exceeding 70 per cent. to 90 per cent. of the total number of white cells, and no immature leucocytes are usually present. For the same reason the number of platelets are decreased and may be absent. This change appears late in

the disease. Strain (36) reports a case of aplastic anaemia which, he observed until death took place, and in which the platelet count was never diminished. There were no haemorrhages.

Pathology. On post-mortem examination (and on biopsy in a few reported cases) the condition of the bone-marrow varies from a mild degree of hypoplasia to one of complete aplasia. In an advanced case of aplastic anaemia the character of the bone-marrow had completely changed, the normal marrow being replaced by fat. Microscopically there is complete absence of all cells such as nucleated red cells, granulocytes, and myelocytes, and the megakaryocytes are diminished in number; actually this complete picture is seldom seen, as Sheard (68) points out, since some of the marrow, especially in the cancellous bones such as the sternum and ribs, often remains active. Further, on examining the marrow in the long bones, for example, in the femur, small scattered red areas of active marrow are often seen, showing that the whole marrow has not ceased to function. An account of the post-mortem appearance of cases 2 and 3 in our series tallies with the above description.

Minot (45) refers to a case in which the marrow was hyperplastic, yet the blood examinations had been those of aplasia. Such a state of affairs is probably dependent on some process that depresses the blood-cell formation, but that does not destroy the marrow.

There may be haemorrhages into the skin, from any of the mucous membranes, or into the serous coverings of the viscera. There is, however, no evidence of blood destruction, and haemosiderin is generally absent from the tissues. If it is present it is due to destruction of blood from a haemorrhage.

Owing to defective blood-supply various internal organs will be affected with fatty degeneration.

DIFFERENTIAL DIAGNOSIS

(a) *From pernicious anaemia.* Since the liver treatment of pernicious anaemia has proved so successful, the differentiation between this disease and aplastic anaemia is now of even greater importance, though it must be remembered that a pernicious-like blood picture is not necessarily indicative of a specific disease, but may have other causes.

The chief diagnostic criteria of pernicious anaemia, apart from the clinical features, are the increased average size of the diameter of the red cell, with a colour index of one or over, and evidence of attempted regeneration of the erythrocytes, with an increase in the numbers of the reticulocytes soon after the haematinic factor has been given. Excess of urobilin is found in the urine, stercobilin in the faeces, and bilirubin in the blood, giving a positive indirect Van den Bergh's reaction. It is true that the erythropenia of pernicious anaemia is due to a diminished production of red cells

by the marrow, and not to an increased destruction in the blood-stream, yet the signs quoted are present in most cases; and they are in part at any rate due to haemolysis, and their presence is a help in the differential diagnosis. In aplastic anaemia haemolysis never occurs.

Achlorhydria is present in almost every case of pernicious anaemia. Glossitis and symptoms of subacute combined degeneration of the cord do not occur in aplastic anaemia. In the therapeutic test the liver or stomach preparation must be active, given in adequate doses, and in the absence of sepsis. It is closely followed by a reticulocyte response, and later by clinical and haematological improvement. Haemorrhages into the skin and other organs with a thrombocytopenia, and a leucopenia with a relative lymphocytosis, are common to both aplastic and pernicious anaemia, though the excessive reduction in granulocytes that is sometimes seen in the former is never present in the pernicious variety.

There may be some difficulty, however, in pernicious anaemia where there is some aplasia of the bone-marrow. This condition may occur, when the disease is progressing rapidly; is not under suitable treatment; or when severe sepsis is present. In the literature of aplastic anaemia cases are sometimes reported of this disease, when in reality they are pernicious anaemia with a temporary aplasia. A post-mortem examination of a case of pernicious anaemia with evidence of aplasia, generally shows a hyperplastic marrow. Sometimes, however, portions of the marrow may show aplasia, and occasionally the whole marrow may be in this condition. Witts (61) says that if in this disease a thorough examination is made of the marrow on autopsy some areas of complete aplasia are always found.

(b) *From haemolytic anaemia.* Aplastic anaemia and chronic haemolytic anaemia, both uncommon diseases, must be distinguished one from another. The latter occurs often, as Witts says (62), as a familial disease, as acholuric jaundice, icterus gravis neonatorum, erythroblastic anaemia of infancy; as well as by infections of the anaerobic streptococci and *B. Welchii*; in certain complications of syphilis and malaria; occasionally in Hodgkin's disease and lymphatic leukaemia, and in the haemolytic anaemia of pregnancy (63).

The essential difference between the two diseases is that in aplastic anaemia the lesion consists of the inhibition of the bone-marrow, whereas in haemolytic anaemia it is the breakdown of the erythrocytes, which are more fragile than normal, in the blood-stream; the bone-marrow meanwhile working overtime as shown by the pouring out of immature cells reticulocytes, normoblasts, and even megaloblasts. Jaundice of the non-obstructive type; a leucocytosis with an excess of granulocytes; no marked falls in platelets; and sometimes enlargement of the spleen, are further guides in the differentiation of these two conditions.

(c) *From aleukaemic leukaemia.* Aplastic anaemia may be simulated by leukaemia of the acute lymphoid type, and by the chronic variety which has been treated by radiation or benzol, or by leukaemia with terminal

sepsis, through which the white cells have been reduced. In the aleukaemic stage of leukaemia the blood count may resemble aplastic anaemia, especially in the rare type in which the round-cell infiltration is exclusively or predominantly in the bone-marrow. Still even then, some abnormal cells such as the large lymphocyte with a pale, possibly lobulated nucleus, and signs of attempted regeneration of the erythrocytes should be seen. And although the actual number of lymphocytes may be decreased, the percentage should be 90 per cent. or over, whereas in aplastic anaemia it is seldom so high.

In most cases of the aleukaemic stage of leukaemia there is some enlargement in the lymphatic glands and spleen. Nevertheless, it may be impossible to differentiate in a few cases the two conditions until the marrow itself has been examined.

Abt (69) has reported the case of a girl, aged 5, with profound anaemia and palpable glands in the neck, together with slight enlargement of the liver and spleen. She had some purpuric spots on both lower extremities, with bleeding from the nose. There was a persistent leucopenia with a large percentage of lymphocytes. A diagnosis of aplastic anaemia was made. On autopsy, the medulla of the tibia was found to be filled with closely packed mononuclear cells replacing the bone-marrow. A rib, however, contained normal marrow tissue. The same authority has quoted a case originally reported by Senator, of a boy aged 13, who suffered from a progressive anaemia, and whose leucocyte count was normal in numbers, but with a lymphocytosis of 83 per cent. No enlarged glands were felt. On autopsy a diffuse lymphoid change in the bone-marrow was found. This type of leukaemia chiefly affecting the marrow, though rare, is more common in children, whereas aplastic anaemia occurs chiefly in adults.

The aleukaemic state may be but a phase in lymphatic leukaemia, and a change from a doubtful to a typical blood picture may occur, which will set any doubts as regards diagnosis at rest. This point is illustrated by a report by Rowlands and Simpson (70) of a woman aged 59, who had some slight enlargement of the glands on both sides of the neck, in the axillae, and groins. There was a leucocyte count of 8,200 per c.mm., with 46 per cent. neutrophils, and 45 per cent. small lymphocytes, together with a secondary anaemia. This aleukaemic phase lasted for nine months, when the white cells rose to over 70,000 per c.mm., 93 per cent. of which were lymphocytes.

(d) *Anaemia which does not conform to any particular group.* Witts says that in infancy and childhood the erythron is more labile. Plastic and aplastic groups with intermediate forms of a hypoplastic type occur. Death may result from the complete failure of the marrow, or, more often than in adults, there is a gradual resumption of function.

Such a case is described by Hutchison (71) of a child, who became profoundly anaemic. The blood count was not typical of pernicious anaemia, but approached somewhat to the aplastic type of anaemia. The author, however, puts this aside on account of the high percentage of polymorphs

(79 per cent. in a white count of 4,688 per c.mm.), and is content to speak of it as anaemia gravis. After taking 3 oz. of cooked liver daily for six weeks the boy recovered.

(e) *Replacement of normal marrow-tissue by osteosclerosis and neoplasms.* These diseases may cause symptoms and blood changes of aplastic anaemia. Clinical history, physical findings, blood and X-ray examinations, and the presence of Bence Jones protein in the urine, will help to elucidate the cause. If a metastatic deposit occurs in the bone-marrow, an irritative, hyperplastic reaction of the erythroblastic tissue may occur, which sometimes produces a blood picture hard to interpret.

Prognosis. In idiopathic aplastic anaemia the outlook is almost hopeless, and little can be done to check its downward course. Of the cases of true aplastic anaemia reported in the literature, we have found only five who have had their condition materially benefited, and of these two have relapsed and died.

Stewart Harrison (72) reports a remarkable case of aplastic anaemia in a man aged 30, who in the autumn of 1925 complained of breathlessness and undue fatigue. In 1926 his blood count was R.B.Cs. 3,500,000 per c.mm., Hb. 50 per cent.; with no abnormality of the red cells. One year later after treatment with iron and arsenic, his condition was much the same. Subsequently the disease progressed more rapidly, with bouts of fever and an agranulocytosis. A specimen of the marrow taken from the sternum, whilst showing no typical fatty condition of aplastic anaemia, was somewhat deficient in haemopoietic tissue. An intensive course of blood transfusions was started. The blood count increased to normal. Transfusions were then given every two to three weeks, but at the end of March 1931, his condition was deteriorating. He had had 109 transfusions in all.

Parkes Weber (73) has reported a somewhat similar case of a man who developed aplastic anaemia in January 1931, with a red-cell count of 770,000 per c.mm. At the end of six months, after sixteen large blood transfusions, the erythrocytes had risen to 2,800,000 per c.mm.

The first of our series of four cases (38) was a woman who has reacted in a similar fashion to the above cases. She has all the symptoms and signs of aplastic anaemia and was gravely ill. She has been under treatment since last December. Her blood count then was—

R.B.Cs.	Size.	Hb.	C.I.	Reticulo- cytes.	W.B.Cs.	P.M.Ns.	Lympho- cytes.	Platelets.
940,000	7.45 μ	10 %	1.5	1 %	4,800	28 %	71 %	94,000

No signs of regeneration of the red cells were seen in the examination of many films. Nor was there any sign of haemolysis; the Van den Bergh was negative, both direct and indirect. A test meal showed free acid in normal amounts.

Under treatment with daily injections of adrenalin (1/1000), and blood transfusions, she has improved, her present blood count being (three weeks after transfusion)—

R.B.Cs.	Hb.	C.I.	Reticulocytes.	W.B.Cs.	Platelets.
1,960,000	40 %	1.0	0.5 %	4,000	73,000

To keep her blood count up to a reasonable level it is necessary to transfuse her about once a month (if this is not done her haemoglobin sinks to about 10 per cent. and the red cells to about a million). It is intended to continue this, together with the adrenalin injections, and up to the present she has had six blood transfusions.

Herrman (74) has written of a case of aplastic anaemia in a child four years of age, who had a blood count of R.B.Cs. 750,000 per c.mm., Hb. 25 per cent.; and W.B.Cs. 2,500 per c.mm., of which 25 per cent. were polymorphonuclear cells, and 72 per cent. small lymphocytes. There were no signs of regeneration of the red cells. The child, after a blood transfusion, became apparently well. She relapsed, however, and died four years after the commencement of the illness. Unfortunately no autopsy was allowed. The difference between these and the majority of cases of aplastic anaemia consists in the degree to which the marrow may be stimulated to produce enough red cells to keep the body alive.

Gibson's (75) case is an interesting one of a girl, aged 11, who suffered from aplastic anaemia of an advanced type, and who recovered and kept in good health for over six years with repeated injections of adrenalin. In the spring of 1923 she was noticed to look pale and to bleed easily. The blood count then was 1,990,000 per c.mm., Hb. 42 per cent., W.B.Cs. 4850, of which the granulocytes were only 12 per cent. and the lymphocytes 87 per cent., with slight signs of regeneration of the red cells. In spite of treatment by arsenic, exposure to X-ray radiations over the spleen, and seven blood transfusions, she became worse. In December 1924, daily subcutaneous injections of five minims of 1/1000 solution of adrenalin were started, with great improvement, and by July she was able to take part in her ordinary life. She continued in good health with the adrenalin injections until her death in 1931 from haemorrhagic chicken pox (76).

Parkinson (77) has described a case of a boy, aged 9, who, although he was diagnosed as suffering from aplastic anaemia, recovered. The attack started with bruising of the arms, back, and legs, with a purpuric rash over the body, and bleeding from the gums. Two weeks later it was noticed that he was pale. A blood count showed Hb. 20 per cent., R.B.Cs. 1,260,000 per c.mm., W.B.Cs. 800 per c.mm., of which the polymorphonuclear cells were 29 per cent. There was some attempt at erythrocytic regeneration. In spite of treatment by the application of X-rays to the long bones, and blood transfusions, no improvement resulted. Some time later, when he was at home undergoing no treatment, he started to improve and made a good recovery.

From the early incidence of the purpuric manifestations it is possible that the boy was suffering from purpura haemorrhagica, rather than true aplastic anaemia. Some of the anaemia may have been due to loss of blood and

the attempt at red-cell regeneration is evidence of this, but most of it and the leucopenia was more likely due to a temporary inhibition of haemopoiesis, which sometimes accompanies purpura haemorrhagica. (An example of the intermediate case referred to above.)

These six cases only serve to emphasize the gloomy outlook in idiopathic aplastic anaemia, if the aplasia of the marrow is at all extensive. It is to be noted that of these cases three occurred in children, in whom the marrow is generally recognized to be more labile than in adults.

Treatment

Until pathogenesis is settled, successful treatment in any of these disorders will depend on the degree of the deficiency of the various elements, the amount of bone-marrow which remains plastic, and the possibility of stimulating such areas as are still active.

The bone-marrow stimulants that are at present known include blood transfusion, small doses of X-rays, protein substances, such as milk, and endocrine extracts, as adrenalin; but if there is anything approaching complete aplasia of one or more of the blood elements such stimulants will be of no avail.

Aplastic anaemia. The instances of the successful treatment of aplastic anaemia have been detailed above. An examination of these reports shows that in all, the condition became one of hypoplasia rather than aplasia. This is borne out, not only by the blood counts, but by the record of the examination of the bone-marrow during life in Stewart Harrison's (73) case. It showed, not the typical replacement by fat, but more or less normal haemopoiesis. Moreover, it is obvious that, even if the stimulating effect of a blood transfusion on the bone-marrow is taken into account, the degree of deficient production which is compensated for by a blood transfusion of only one pint every two or three weeks (which is also the average length of life of an erythrocyte), cannot be very great.

However, in this practically hopeless disorder, treatment by repeated blood transfusion and daily injections of adrenalin offer the best chance of success. Iron, arsenic, liver therapy, and removal of septic foci are of no avail, although Alpham and Nelson (78) report a case of a man suffering with severe aplastic anaemia, who did not improve with blood transfusions and calf's liver. With massive doses (1000 gr. per day) of foetal calf's liver, however, he recovered, and kept well on a much smaller dose.

Treatment in cases of aplastic anaemia with a known cause is more hopeful if the patients are removed from the cause, e.g., benzol, sufficiently early.

Of the cases of aplastic anaemia which occurred at New Jersey among the workers employed in painting dials of instruments with a luminous paint containing small amounts of radium, Flynn and Seidlin (79) have treated three with success by injections of parathormone. The radio-active sub-

stance was found to be stored in the bones and viscera of the patients, in the same way as lead in chronic lead poisoning. Injections of parathormone caused an increase in the excretion of lead, and a similar result was hoped for and obtained in these cases of aplastic anaemia.

Agranulocytic angina. Little success has attended the performance of blood transfusion in this disorder.

Both Zikowsky (80) and Freidemann (81) report a successful issue after treatment by X-rays; with small doses of X-rays over the long bones, the former caused the appearance of mature granulocytes in the blood, and his patient recovered. Friedemann reports four cases of cure by X-ray applications to the long bones. He gave 5 per cent. of an erythema dose through a hard filter. In the first hour after irradiation his patients showed an appreciable increase in granulocytes.

Gordon (82) brought about a successful issue by the injection of 2 c.c. of turpentine into the hip with abscess formation following—a procedure that resulted in a leucocytosis of 8,000 per c.mm. Some recoveries have now been recorded without any specific treatment, and it seems unlikely that these remedies would have availed in the vast majority of cases.

Idiopathic purpura haemorrhagica. Since the platelet is a less vital cell than the erythrocyte and granulocyte, the outlook here is less gloomy. Moreover, treatment by splenectomy at one time promised a degree of specificity, and although, as is indicated above, it is by no means an invariable success, yet most authorities recommend it in the recurrent or chronic cases, where life is repeatedly endangered, or a normal existence is made impossible.

The results of splenectomy have been reviewed by Whipple (83) in America, by Spence (48) in England, and by Quenu (84) in France. All these observers come to similar conclusions, i.e., that there is a high percentage of successes in the chronic cases, but if the operation is performed during an acute phase there is a very high mortality. The operation of splenectomy in an acute attack of purpura haemorrhagica obviously demands very careful preparation of the patient, and a high degree of surgical skill—but given these factors, it is difficult to account for the great operative risk. Le Marquand and Mills (85) in reporting a successful result from splenectomy in an acute attack, suggest that earlier operation would give better results.

It is not yet possible to distinguish before operation between the type of purpura haemorrhagica in which splenectomy is likely to succeed, and that type in which it is likely to fail; but a consideration of all the reported cases gives one definite contra-indication.

Splenectomy should not be performed if the blood picture suggests that there is deficient production of the other blood elements, i.e., (1) if the red cells and haemoglobin show a greater reduction than the haemorrhages would warrant, (2) if there is a marked leucopenia, notably in granulocytes, and (3) if in spite of these reductions, there is no evidence of active haemopoiesis. These cases are allied to aplastic anaemia, and splenectomy does

not improve their prognosis; an example of this is provided by the second case reported by Spence (48).

For immediate relief transfusion is a life-saving operation, and although its effect is transient, yet if it is repeatedly performed, it tides the patient over the attack. Some authors have recorded recoveries following the exhibition of liver in this disorder, but Witts (86) states the general opinion that it is of no effect. Hayes Smith (87) has reported success with liver in aplastic anaemia in a child, but it is likely that his case was one of idiopathic purpura haemorrhagica with some evidence of agranulocytosis. It is notoriously difficult to assess the effect of a remedy in a disorder, which so often ends in recovery.

Here again, as in agranulocytic angina, some authors have recorded improvement following a stimulating dose of X-rays to the long bones. It is interesting to note, from an aetiological point of view, that other bone-marrow stimulants besides these, such as adrenalin, or a foreign protein such as milk, appear to exercise a beneficent influence on the course of the disease.

Pathogenesis

As in every disorder in which the aetiology is obscure, there are many theories of causation. The greater the obscurity of the condition, the stronger is the temptation to theorize. Such theories are only valuable if they embrace all the known facts, and if they stimulate further investigation. The more important theories will be briefly discussed.

1. *Aplastic anaemia is a sub-type of pernicious anaemia.* This theory has had a good deal of support in the earlier literature (88, 89) of the subject, but we believe it is impossible, in view of the great increase in our knowledge of pernicious anaemia, to produce any evidence in its favour. The symptom-complex, the blood picture, and the morbid anatomy of the two conditions are so dissimilar, that confusion between them is unlikely.

2. *Aplastic anaemia is secondary to repeated and persistent haemorrhage.* This theory crops up continually in the literature, usually to be criticized adversely. The evidence, both experimental and clinical, against haemorrhage as an important aetiological factor, is very strong. It may be briefly stated: 1. Prolonged experimental bleeding in animals results in a true secondary anaemia with evidence of blood regeneration (90). A leucocytosis is commonly produced and the typical post-mortem picture is one of hyperplasia of the bone-marrow (91). 2. Prolonged and severe haemorrhage is often observed clinically, without any suggestion of the development of an aplastic blood picture. 3. Nearly all the recorded cases of aplastic anaemia have no prodromal haemorrhage, and even when a haemorrhage occurs, it is to be regarded, not as a first cause, but as the first symptom. Ehrlich's (51) classical case was a woman, in whom severe uterine haemorrhage was the prodromal symptom.

3. *Aplastic anaemia results from the direct action of a toxin on the bone-marrow.* It has been shown above that depression of all haemopoietic activity may be produced by the action of toxins, both chemical and bacterial. It is not surprising, therefore, that idiopathic aplastic anaemia has been attributed by many observers to the action of some unknown toxin on the marrow.

An aplastic blood picture and an aplastic or hypoplastic bone-marrow have very occasionally been reported in such common infections as pneumonia, typhoid fever, diphtheria, malignant endocarditis, and in overwhelming sepsis. Although in typhoid fever an anaemic blood picture and a hypoplastic bone-marrow are moderately common (60), yet it is difficult to believe that the toxins of pneumonia and diphtheria, for example, will in such extremely rare instances act as direct bone-marrow poisons. It is preferable to believe that in those occasional cases there is already present some unsuspected defect of haemopoiesis.

That this may be true is suggested by Gibson's case (75, 76) of exceptional interest, where a child, in whom a hypoplastic anaemia was known to have been present for six years, succumbed in the end to an attack of chicken-pox. It is reasonable to assume that if the defective condition of the bone-marrow had not been recognized before the onset of the chicken-pox, this case would have been described as one of aplastic anaemia developing secondarily to an infectious fever.

Before these cases of secondary aplastic anaemia developing in the course of an infection can be accepted as caused by the specific toxin, it has to be shown (as in typhoid fever) that the disease normally results in an anaemia of hypoplastic type.

There is, too, little evidence in the clinical course of idiopathic aplastic anaemia or at autopsy of any sources of infection.

The absence of a positive blood culture, and the failure to discover any source of sepsis *post mortem*, are constant in all records. We do not think that the morbid anatomy of the bone-marrow is particularly suggestive of an acute and overwhelming infection. The replacement of the haemopoietic tissue by fat, and the absence of any normal cellular reaction or evidence of bacterial invasion, seem to us strong evidence against this theory. There are, however, two references in the literature which appear to favour an infection of the bone-marrow. Stewart Harrison (*vide supra*) examined the bone-marrow in his case of mild aplastic anaemia and found a marked eosinophilia and some round-celled infiltration. Dyke (92) has observed three cases in which he found organisms in the bone-marrow. One was a case of myeloid leukaemia with a secondary aplasia developing—miliary tuberculosis was discovered *post mortem*, with tubercles in the marrow of the femur. Another, in which all the bones except the femur presented the normal picture of aplasia, but the femur showed a recent haemorrhage with streptococci in the haemorrhagic areas. The third case showed coliform bacilli in the haemorrhagic areas in the femur. These

observations, though solitary and atypical, are extremely interesting, but the evidence seems good that the presence of micro-organisms in the bone-marrow was a secondary phenomenon in each case.

A minor point which is also against the toxic theory, is that those milder cases of benzol poisoning which do not die, regain, as one would expect, a normal blood picture; whereas those of mild idiopathic aplastic anaemia in the adult, which have been followed for several years (Gibson, Stewart Harrison), continue to present a picture of moderate aplasia. This continuance of moderate aplasia for many years is extremely difficult to reconcile with the toxic theory. It is difficult to conceive a toxin which continues to poison the marrow over a prolonged period such as this, without any other evidence of its activity. Alternatively, if the toxin has ceased to act, it is impossible to account for the failure of the unaffected haemopoietic tissue to regenerate completely.

Therefore we conclude that, while it is not easy to exclude a toxin which has a selective action on the bone-marrow, yet there is no good evidence of it. Pernicious anaemia was very generally ascribed at one time to the action of a toxin on the bone-marrow, and it is but natural that recently-acquired knowledge of this disease should be used to throw fresh light on other disorders of the haemopoietic system.

Another conception of these haemopoietic deficiencies which accords better with modern theories of haemopoiesis is developed below.

4. *Aplastic anaemia is due to defect in normal haemopoiesis.* To Frank (93) belongs the credit for the idea that in aplastic anaemia there is an inherent deficiency in the haemopoietic system. He re-named the disorder, aleukia haemorrhagica, a name which is not particularly satisfactory, as it only indicates two of the three blood elements which are deficient.

He included, with aleukia haemorrhagica, two types of thrombopenia, essential and intermittent; in the first, the platelet deficiency persists without alteration through life or for long periods, and in the second, the condition is intermittent, and after the purpuric condition disappears the platelet count returns to normal.

Most authorities do not agree to this distinction, since in the second group Frank has included those purpuras in which the defect is now believed to be in the capillary walls.

Moreover, although in these bone-marrow deficiencies occasional cases are described which suggest a congenital and, even more occasionally, an inherited weakness of haemopoietic function, yet there is little evidence of this in the overwhelming majority of reported cases.

The merit of Frank's concept lies in the co-ordination of these conditions, and his insistence on a bone-marrow deficiency. Witts (64), among others, has added agranulocytic angina to the group, and his classification is similar to our own. Rennie (94) attributes aplastic anaemia to a congenital defect of the bone-marrow in the group whose onset is at an early age, while in older persons he attributed it either to paralysis of its activity or to exhaustion.

The knowledge that certain substances are essential for the normal development of the erythrocyte has been recently reviewed by Witts (61), and he suggests that in aplastic anaemia there is lacking some substance which is essential for the normal development of the megaloblast from the reticulo-endothelium of the marrow.

A similar conception has occurred to others, and indeed, if the bone-marrow without obvious cause, and after years of normal functioning, suddenly diminishes its output of certain cells, irrespective of the needs of the body and its own ultimate well-being, it is natural that a reason should be sought in the failure of the mechanism which controls the output of these cells.

The factors which control the development of the blood elements from the primitive stem-cells of the reticulo-endothelial system are unknown, and an attempt to formulate a hypothesis concerning this control must involve several questions.

5. *Are there specific factors for the development of each blood element?* The fact that clear-cut individual types of deficient production of each of the blood elements occur, makes it likely that each element has its appropriate regulators, but the fact (as has already been sufficiently emphasized) that intermediate cases occur, makes it equally certain that these regulating factors are not rigidly selective for any one cell.

It should be remembered that this question has not been settled for pernicious anaemia. Is the leucopenia and thrombocytopenia of this disease secondary to the megaloblastic hyperplasia of the bone-marrow, or dependent upon the absence of the pernicious-anaemia factor which is also essential for the normal production of granulocytes and platelets? Many observers have recorded that treatment with liver produces a rise in the circulating granulocytes and platelets coincident with the improvement in erythropoiesis.

6. *What is the nature of this deficient controlling factor?* There is little evidence as to the nature of the deficient factor. Witts suggests that aplasia of the bone-marrow may possibly result from the absence of certain food substances (61).

Some support for this hypothesis is found in animal experiments. It has been demonstrated in pigeons that a hypoplasia of the bone-marrow can be produced by the simple withdrawal of food for ten to eighteen days; when the pigeons are put back on to their ordinary diet of grain the hypoplastic acellular marrow returns to its normal state in about seven days (95).

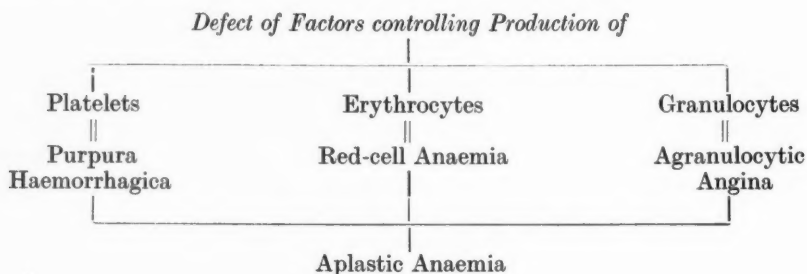
However, the same observers attempted to produce the same condition in rabbits without success.

The alternative hypothesis is that this failure of the reticulo-endothelium to produce normal blood-cells is due to the disturbance of some internal regulating mechanism. On general principles, it would seem likely that there is an endogenous control of haemopoiesis in addition to the exogenous factors, such as vitamins B and C, the active principle of liver, iron, and traces of other minerals which are essential for the normal maturation of the erythrocyte. A vast literature has accumulated concerning the influence of the

endocrine system on haemopoiesis, and we have attempted to review some of this evidence elsewhere (96). Many observers have attributed the cause of such blood-diseases as the leukaemias, polycythaemia, agranulocytosis, chlorosis, and the chronic microcytic anaemia of middle-aged women to some endocrine dysfunction. Castex, too, has collected much evidence to prove that the regulation of blood-production is under the control of the vegetative nervous system and the diencephalo-pituitary apparatus (97).

These ideas are still hypothetical, but it appears preferable to us to attribute these deficiencies of the bone-marrow, idiopathic aplastic anaemia, agranulocytosis, and idiopathic purpura haemorrhagica, to the absence or defect of the essential controlling factor, whether endogenous or exogenous, rather than to implicate a toxin whose existence seems improbable.

The pathogenesis of these aplastic or hypoplastic conditions of the bone-marrow may be put in diagrammatic form:



Nomenclature

Frank originated the term *myelophthisis* for these primary deficiencies of the bone-marrow and, in the present state of our knowledge, it is an adequate name, but later authorities have debased its usage, so that it is now commonly employed to describe those secondary aplasias of the bone-marrow in which the myeloid tissue is invaded by other cells, as in carcinomatosis or osteosclerosis. If the name is restored to the author's original conception, it is possible to unify the terminology of all these bone-marrow deficiencies.

Aplastic anaemia, in which all three elements are deficiently produced, should now be known as *myelophthisis*; agranulocytic angina, in which there is defective formation of granulocytes, as *granulophthisis*; the rare cases of pure red-cell anaemia, as *erythrophthisis*; and one group of purpura haemorrhagica as *thrombophthisis*. This nomenclature emphasizes the connexion between these disorders, and indicates their origin as bone-marrow deficiencies. It is obviously not possible at the moment to suggest a nomenclature which accurately defines their exact pathogenesis.

Summary and Conclusions

1. A group of bone-marrow disorders in which the blood elements are deficiently produced includes agranulocytic angina, idiopathic purpura haemorrhagica, pure red-cell anaemia, and aplastic anaemia.

2. All these conditions probably have a common pathogenesis. Intermediate cases are very frequently recorded, and known toxins such as benzol can produce any one of these clinical pictures.

3. In agranulocytic angina the evidence collected indicates that the sepsis in this disorder occurs secondarily to the leucopenia.

4. It is concluded that there are, at least, two types of purpura haemorrhagica, which are not, at present, clinically distinguishable. In one of these types there is deficient production of platelets by the bone-marrow.

5. Only three cases of pure red-cell anaemia have been found in the literature, and these are quoted.

6. The aetiology, signs, symptoms, and differential diagnosis of aplastic anaemia are described in detail.

7. Cases are described illustrating the difficulties of differential diagnosis.

8. The treatment of all these bone-marrow disorders is considered together.

9. The theories of pathogenesis of aplastic anaemia are critically reviewed, and it is suggested that it, and the allied disorders, are examples of bone-marrow deficiencies in which the essential regulating factor which initiates and controls the development of the blood-cells from the reticulo-endothelial system is defective.

10. A new nomenclature which co-ordinates these bone-marrow deficiencies is proposed.

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A CLINICAL AND PATHOLOGICAL STUDY OF BRONCHIECTASIS¹

By H. H. MOLL

With Plates 25 to 28

SINCE the injection of lipiodol into the bronchial tree has been more widely adopted in the diagnosis of chronic pulmonary affections, bronchiectasis has come to be considered a much more common disease than it has been hitherto.

The frequency of bronchial dilatation, and especially of the primary form, was difficult to assess before the condition could be demonstrated by contrast radiography, and statistics had to be based mainly upon post-mortem material and upon clinical observations of physical signs and symptoms, neither of which revealed the real incidence of bronchiectasis. At autopsy only the more advanced cases with marked anatomical changes are observed, while the earlier forms are probably missed owing to the difficulty in recognizing the condition, and for this reason autopsy observations of bronchiectasis are comparatively rare. Thus, during the past twenty years, out of 12,225 post-mortem examinations made at the General Infirmary at Leeds, only fifty-five cases (i.e. 0.4 per cent.) of bronchiectasis have been recorded. This refers to primary or idiopathic bronchiectasis and does not include tuberculous bronchiectasis or bronchial dilatation secondary to either carcinoma of the bronchus or to pressure of the bronchus caused by aneurysm or growth. Willigk (Ochsner (2)) found bronchiectasis in about 8 per cent. of 4,547 post-mortem examinations, while Biermer (1) found it in 2 per cent. out of 400. Undoubtedly these figures do not disclose the real incidence of bronchiectasis, if one may judge by the relative frequency with which the condition is now being observed clinically by means of an intra-bronchial injection of lipiodol.

Although absolute figures are difficult to obtain, as they depend upon the thoroughness with which cases are investigated, a general opinion is expressed in recent literature that bronchiectasis is a common type of disease, and Ochsner (2) even states that it is the most frequently encountered pulmonary affection, occurring more frequently than pulmonary tuberculosis.

Certainly bronchography should be adopted in every case of chronic pulmonary disease in which the diagnosis is at all doubtful, and not too much reliance should be placed on physical signs or on an ordinary X-ray

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examination. The physical signs of bronchiectasis are notoriously misleading; often a wrong diagnosis of chronic bronchitis or of pulmonary tuberculosis is made, and it is indeed unfortunate to find that many patients with bronchiectasis have spent months and sometimes years in sanatoria before the true condition was discovered. An ordinary X-ray examination may often be insufficient to reveal bronchial dilatation, as this may be obscured by the heart shadow, by the dome of the diaphragm, or by fibrosis. In some cases, the lungs are surprisingly translucent to the X-rays, and yet on taking a bronchogram a well-marked bronchial dilatation can be demonstrated. Hartung (3) made a comparative study of the ordinary and contrast methods of radiological examination in seventy-two cases of bronchiectasis and found that a correct diagnosis by ordinary X-ray examination could be made in only twenty cases.

The present study has been based on fifty-five autopsy observations and on thirty-seven clinical cases examined by contrast radiography.

Types

The various forms of dilatation which are observed clinically after injecting lipiodol into the bronchial tree are very similar to those which are described at autopsy and may be classified as: (1) the uniform, tubular or cylindrical, (2) the fusiform or glove finger, (3) the globular or sacculated, and (4) the moniliform or bead-like. In addition, intermediate forms are also frequently found between the tubular and saccular.

Uniform or cylindrical dilatations are those where the tubular form is maintained, but the bronchial ramifications retain the size of the larger divisions instead of undergoing diminution in their diameter (see Plate 25, Fig. 1). This type is often accompanied by adhesive pleurisy and emphysema, tends to be bilateral, and affects the lower lobes more than the upper.

The fusiform dilatations tend to a progressive increase in size towards their terminal extremities, thus giving rise to a bulbous appearance or that of the fingers of a glove (see Plate 25, Fig. 2). They are often found inside a collapsed lobe, and are in fact the commonest type of 'atelectatic' bronchiectasis.

The globular or sacculated form of bronchiectasis is one which often presents the most extreme degree of bronchial dilatation. The dilated extremities give rise to rounded cavities which may be either single or multiple, and according to their size may appear on the skiagram as a bunch of grapes (see Plate 26, Fig. 3), or have a honeycomb appearance. Saccular dilatations do not as a rule exceed one-third to half an inch in diameter, but sometimes they may reach the size of a small tangerine orange (see Plate 26, Fig. 4). The pulmonary tissue around the sacs is usually in a state of advanced fibrotic induration which may affect the lower lobe only or the whole of one lung.

By the irregular contraction of the strands of fibrous tissue connected with it, a saccular bronchiectasis may become extremely irregular in shape and, by being pinched in one place and pulled in another, the walls may

come to have a trabecular appearance. Partial sacculation may sometimes be observed on one side of the tube, but the remainder of the circumference retains its normal shape. This gives the bronchus an irregular and worm-like appearance, and this type may often be found in the intermediate forms which are developing from the tubular into the saccular type (see Plate 27, Fig. 5).

In some cases saccular bronchiectasis may be entirely confined to one upper lobe, thus simulating a tuberculous excavation. The moniliform or bead-like dilatations are those occurring at intervals in a bronchial tube, while the size and shape of the bronchus is normal between them (see Plate 27, Fig. 6). Unlike the saccular type which affects the terminal bronchi, and in which it is rare to find any continuation of the bronchus on the terminal side beyond the dilatation, the moniliform variety occurs along the course of the bronchi and near the bifurcation of the secondary bronchial branches; the appearance is very similar to that of congenital 'berry' aneurysms of the cerebral arteries.

The tubular, saccular, and intermediate forms between the tubular and the saccular, are the most common types of bronchiectasis, while the fusiform, and especially the moniliform types, are distinctly less frequently found (see Table I).

TABLE I

Type.	Number of Cases (32).
Tubular	7
Marked saccular	9
Early saccular	5
Fusiform	4
Moniliform	2
Intermediate	5
	<hr/> 32

There are two types of bronchiectasis which have been better recognized since bronchography has come into use, to wit, the atelectatic type and the dry (non-suppurative) haemorrhagic type. With regard to the former, the condition is usually characterized by the presence of bronchiectasis inside a triangular shadow near the mediastinum and at the base of one lung. If on the left side, this shadow may be seen on an ordinary skiagram as a denser area inside the heart shadow, while if it is on the right side it obliterates the cardio-hepatic angle. It is a right-angled triangle with its right angle near the mediastinum and the hypotenuse extending from the hilum of the lung to the base (see Plate 28, Fig. 7).

On injecting lipiodol into the lung this shadow is seen to contain a bunch of bronchiectasis, often of the fusiform type. In many cases the dilated bronchi are bunched together, suggesting that the lower lobe has become collapsed, while those of the upper lobe are spread out fan-like, indicating that the upper lobe has become emphysematous and has expanded in order to fill up the space left unoccupied by the collapsed lower lobe. In some cases the collapsed lobe has been seen to re-expand (Sparks (4)), while in other cases the lobe becomes permanently indurated by dense fibrous tissue.

The condition has been described under the name of 'atelectatic' bronchiectasis, and certainly the early history of chest trouble (often dating from a few weeks after birth) which is frequently found in these cases suggests that atelectasis or imperfect clearing of an early attack of pneumonia may have been the primary cause. Moreover, the anatomical distribution of the bronchi of the second order in close proximity with the mediastinal pleura favours the spread of infection from the bronchi to the pleura and the onset of a chronic adhesive mediastinal or interlobar pleurisy with secondary interstitial pulmonary fibrosis.

The dry form of bronchiectasis is characterized by a complete, or nearly complete, absence of expectoration and by a great tendency to repeated and often profuse haemoptysis. Bezançon and Azoulay (5) first called attention to this condition in 1924 when they published two cases. Since then other cases have been reported by Reinberg, Burrell and Trail, and by Scott Pinchin and Morlock (27). Haemoptysis is often the only symptom of this condition and raises the suspicion of pulmonary tuberculosis, in spite of the fact that an ordinary skiagram fails to reveal any definite abnormality of the lungs and the sputum is constantly negative.

In the present series of cases two cases of dry bronchiectasis have been observed. In one case a bronchogram revealed marked fusiform bronchiectasis behind the heart shadow, while in the other there was early saccular bronchiectasis at the extreme base of the left lung, the bronchial dilatation being hidden by the dome of the diaphragm.

Seat and Extent of the Dilatations

Bronchiectasis in its early stages is usually a unilateral affection and limited to one lobe, while later it becomes bilateral. This is borne out by a comparison between autopsy cases, where the condition is seen in the more advanced stage, and cases investigated by bronchography, where the earlier forms may be observed (see Table II).

TABLE II

Extent of lesion.	Autopsy cases (55).	Lipiodol cases (37).
Unilateral	28 or 50.9 %	25 or 67.5 %
Bilateral	27 or 49.1 %	12 or 32.5 %

The figures given above conform with those of other observers. Thus Hedblom (6) investigated sixty-three cases by bronchography and found a unilateral affection in forty-five cases, or in 70 per cent. of cases, and a bilateral one in eighteen cases, while Lebert (8) in fifty-four post-mortem examinations found a double affection in twenty-six and a single one in twenty-eight. Trojanowski (9) in a series of seventy-four autopsy cases also found unilateral and bilateral lesions in a similar proportion of cases, to wit, thirty-nine cases were bilateral and thirty-five unilateral.

Although in some cases the lung may acquire a remarkable degree of tolerance, there is no doubt that in the majority of cases bronchiectasis is a progressive disease and tends to become more and more extensive through a bronchogenic infection. The opinion that bronchiectasis is as often unilateral as bilateral is probably based on autopsy findings and on clinical observations before contrast radiography came into use. Clinically it is difficult to localize a bronchiectatic lesion on physical signs alone, as these may be transmitted from the diseased to the normal side. Often catarrhal sounds may be heard in the contralateral lung, although on injecting lipiodol no obvious bronchiectasis may be found.

Hedblom (6) found in a series of 316 cases studied without a lipiodol examination that 36 per cent. were diagnosed as unilateral, 28 per cent. were diagnosed bilateral, and 36 per cent. were indeterminate. These figures are in contrast with those of a subsequent series of cases examined by the same observer by means of a lipiodol injection and which showed a marked preponderance of unilateral cases.

Findlay and Delille (7), in reviewing a series of twenty-five cases in children, found even a greater percentage of unilateral cases, i.e. the condition was confined to one lung in twenty cases (80 per cent.). This high percentage of unilateral cases in their series is probably explained by the fact that they were observing the condition at an early stage, as the patients were all children. My series of cases included approximately the same proportion of children as of adults.

As the use of bronchography becomes more widespread it is hoped that it will be possible to diagnose bronchiectasis at an earlier stage than has been done hitherto. Plate 28, Fig. 8 is an example of a localized type of bronchiectasis which was successfully treated by artificial pneumothorax.

When both lungs are affected it is seldom in an equal degree, and it is common to find, after injecting lipiodol, that the bronchiectasis is more advanced in one lung than it is on the other side (see Plate 27, Fig. 5). The left lung suffers more frequently than the right one and, more especially, the left lower lobe is more frequently affected than the right lower lobe. The reason for this is not clear, and it is rather surprising in view of the fact that lung abscess is about three times as common on the right side as it is on the left. Several explanations have been offered, and Sauerbruch believes that as the result of congenital malformation there is more apt to be obstruction in the left bronchus than in the right. Duken is of the opinion that the left lower lobe is involved more frequently than the right because the left bronchus comes off the trachea at a more acute angle than the right, and because the pulmonary artery crossing on the left bronchus produces a slight constriction just before the upper bronchus is given off. Another anatomical reason may be the curved shape of the left bronchus as compared with that of the right, due to the presence of the heart, which prevents free drainage of secretions once the left bronchus has become infected.

In a combined series of fifty-three cases of unilateral bronchiectasis, either observed at autopsy or examined by a lipiodol injection, the left lower lobe was found to be affected nearly twice as frequently as the right lower lobe.

Bronchiectasis may affect any part of the lung, but in more than half the number of cases the condition was found to be limited to the base of the lung. The condition was only rarely confined to the upper lobe, and when apical bronchiectasis did occur it was more frequently found on the right side. In more than half the number of cases the bronchiectasis was confined to a lobe, this being somewhat encouraging from the point of view of treatment. The following table shows the seat of the lesion in fifty-three cases of unilateral bronchiectasis.

TABLE III

Seat of lesion.	Autopsy cases (28).	Lipiodol cases (25).	Total (53).
Left lung, upper lobe	0	1	1
„ lower lobe	11	8	19
„ whole lung	5	5	10
Right lung, upper lobe	4	2	6
„ middle lobe	1	2	3
„ lower lobe	5	6	11
„ whole lung	2	1	3

Note.—‘whole lung’ means that more than one lobe was affected.

In this combined series of 53 unilateral cases of bronchiectasis the condition was confined to the upper lobe in 7 cases or in 13·2 per cent., to the middle lobe in 3 cases or in 5·6 per cent., and to the lower lobe in 30 cases or in 56·6 per cent.; a diffuse lesion affecting more than one lobe was found in 13 cases or in 24·6 per cent.

Pathogenesis

Some cases of bronchiectasis carry their own explanation of the mechanism of production. Congenital narrowing, cicatricial stricture, lateral pressure from an aneurysm of growth, internal obstruction due to tumours, and particularly to the impaction of foreign bodies, are all occasional causes of bronchial dilatation.

In all cases of partial bronchial obstruction a bronchial dilatation occurs distal to the obstruction, while complete closure of the bronchus leads within twenty-four hours (Lichtheim) to atelectasis of the corresponding lung parenchyma with purulent secretion within the obstructed bronchi. After a few weeks the bronchi near the site of the obstruction dilate. Raynaud has also shown that the dilatation occurs both distal and proximal to the obstruction and in the neighbouring unobstructed branches. Cases of bronchiectasis due to bronchial stenosis are relatively rare, and there still remains a large group of primary bronchiectasis requiring elucidation.

Congenital bronchiectasis probably also forms a distinct group. A foetal bronchiectasis was first described by Grawitz, who contended that bronchi-

ectasis was the result of congenital cystic changes in the lung. Sauerbruch also states that there is a congenital element of weakness. Duken believes that a few cases of bronchiectasis are congenital. He considers that the predisposition to bronchiectasis is congenital, as bronchiectasis is often associated with other congenital abnormalities such as idiocy and imbecility. Henschen and Willy Meyer consider a congenital malformation as a possible cause of bronchiectasis. Hedblom (10) states that it is extremely difficult to ascertain the relative frequency of congenital bronchiectasis, as the symptoms are the same as in the acquired type. In many cases the condition may only accidentally be found at autopsy and may never have given rise to symptoms during life. Congenital bronchiectasis may be suspected when there is a continuous history of chest trouble since birth, although some cases may become infected only later in life and be quiescent during a number of years.

The pathogenesis of congenital bronchiectasis has been variably described (10) as being due to an arrested development (Kaufmann), to a collection of fluid in the foetal bronchioles (Grawitz), to a foetal adenoma (Stoerck), to intra-uterine syphilis (Balzer and Grandhomme) and to mechanical overcrowding of the left main bronchus during development (Sauerbruch).

The position of the bronchial dilatations near or at the bifurcation of the secondary bronchi observed in one case of moniliform bronchiectasis (see Plate 27, Fig. 6) suggests congenital malformation or weakness of the wall similar to that which occurs in 'berry' aneurysms of the cerebral arteries.

With regard to the mechanical factors causing bronchiectasis, much has already been written and great ingenuity has been displayed in explaining their action. Distension from within has been ascribed to increased pressure from violent expiratory efforts such as prolonged coughing or from pent-up secretions.

As Hedblom points out (10) it is unlikely, however, that violent expiration plays any part at all, as with closed glottis the pressure is raised both within and outside the bronchus.

Deep inspiration just preceding coughing, instead, produces a maximal difference between the intrabronchial and intrapleural pressures. Increased intrabronchial pressure may play some part in the production of the tubular and diffuse types of bronchiectasis, although even in cases of bronchial obstruction it has been noted that bronchial dilatation may occur on the proximal as well as on the distal side of the obstruction and in the opposite unobstructed lung.

Laennec believed that bronchial dilatation was, for the most part, due to distension of the bronchial tubes from the accumulation of mucus or secretions in their interior, but his theory does not account for the occurrence of 'dry' haemorrhagic bronchiectasis in which there is no stasis of secretions.

Another mechanical explanation of bronchial dilatation is that it may be due to traction of the bronchial wall from without, either from scar tissue

retraction or because the support to the outside of the bronchus is lessened as the result of atelectasis. Corrigan (11) was the first to consider that cirrhosis of the lung was the cause of bronchiectasis. His view was that dilatation was in part due to the retracting force of the solidified lung expanding the bronchi, and in part to compensatory enlargement of these tubes occurring chiefly during the act of inspiration, in order to fill the space imperfectly occupied by the retracting lung. Since his time many other authors have upheld that cirrhosis of the lung may play an aetiological role. Although the more advanced cases of bronchiectasis, and especially the sacculated types, are often associated with chronic indurative or cirrhotic changes in the lungs, this is not always the case, and the lung surrounding the dilated bronchi may be normal or emphysematous. Moreover, not all cases of pulmonary fibrosis lead to bronchial dilatation, and Bastian (12) failed to find bronchiectasis in as many as 20 per cent. of cases of pulmonary cirrhosis.

Lebert, Drummond, and King (13) have attached much importance to the occurrence of pleural adhesions either locally or generally. Lebert has described a 'pleuritis profunda' setting up a proliferative irritation in the pleuro-pulmonary connective tissue. Lebert states that owing to the rigid connexion of the surface of the fibrosed lung with the chest wall, not only will the spontaneous shrinking of the fibrous tissue lessen the distance between the chest wall and the bronchial wall, but every inspiratory effort of the former will take effect in dilating the cavity of the bronchus.

While these mechanical processes may play some part in the production of bronchiectasis, it is suggested here that none of them has the importance of a primary factor, and that bronchial dilatation is mainly brought about by an inflammatory process weakening the bronchial wall. This view is not new, and Stokes in 1837 expressed the opinion that bronchial dilatation was due to impairment of elasticity and of muscular contractility by inflammation. Wilson Fox (16) also stated very clearly that the mechanism of dilatation was due to expansile influences of cough on tissues weakened by inflammation, and that the presence of induration in the surrounding pulmonary tissue was simply a condition tending to perpetuate the dilatation, but that it was not the chief factor in its production.

The important role played by infection in the production of bronchial dilatation has never been so clearly demonstrated as recently, when it has been possible to observe an analogous condition occurring in a rigid organ such as the parotid gland.

Payne (14), Pyrah and Allison (15) on injecting lipiodol into the parotid gland have observed, in cases of chronic parotitis, tubular and saccular dilatations of the ducts and alveoli strictly comparable with bronchiectatic dilatations.

Weakening of the bronchial wall from inflammatory processes may be due to destruction of the mucosa of the muscular coat, or of the elastic fibres.

In the early stages of bronchiectasis the condition may be simply a loss of tone of the bronchial wall leading to temporary dilatation. Ochsner (2) mentions four cases in which bronchial dilatation was definitely diagnosed both clinically and radiographically and in which radiological evidence of bronchiectasis disappeared after adequate therapy. In all probability a functional dilatation of the bronchi always precedes any anatomical change. The dilatation is probably caused by atony of the bronchial musculature, which has been acted upon by bacterial toxins, aided by the stagnation of retained secretions.

In the advanced stages the bronchial musculature and elastic fibres as well as the mucous glands and even cartilage are destroyed, the entire wall being replaced by fibrous tissue.

In the smaller tubes the elastic fibres are probably the structures which are chiefly concerned in resisting dilatation. Miller (25), in a case of acute bronchiolectasis, or honeycomb lung, has described a uniform stretching and thinning of the elastic laminae. A burst may also take place at one particular point, the laminae being to all appearances torn through.

In the larger bronchi loss of tone of the muscular coat is probably the most important factor. Hudson (28), by taking rapid serial radiograms, has been able to make some interesting observations on the presence of motor phenomena in the tracheobronchial tree. Already laryngologists had been able to note that the bronchi are not rigid and immobile tubes but that they widened and narrowed when they were observed through the bronchoscope. Hudson, by taking a series of exposures at the rate of one per second after the lung had been injected with lipiodol, was able to demonstrate that the bronchi are subject to definite movements of widening and lengthening during inspiration and of narrowing and shortening during expiration; he also noted that in bronchiectasis these movements were lost. Reinberg (26) has observed in the trachea of the goose also wavy contractions of the entire tube of a true peristaltic nature, and investigations in numerous human cases has led him to believe that the tracheobronchial tree in man is also endued with the same peristaltic function; he has also noted that these movements are greatly impaired in bronchiectasis, so that an opaque mixture may remain in the cavities for weeks and months.

From these observations it would appear that there is a good deal of evidence to show that in the early stages of bronchial dilatation the bronchi lose their normal contractile movements and remain in a state of paralytic dilatation, while later the bronchial walls may become totally destroyed and replaced by scar tissue.

Further support to the infective theory of bronchiectasis is given by the frequency of antecedent respiratory infections and by the high incidence of nasal infections in this disease.

Hedblom (10) states that in the vast majority of cases infection precedes or is concurrent with the mechanical factors, and that in 55.5 per cent. of 552 cases reviewed by him a preceding illness or ascertainable cause could

be established, such as bronchitis and recurrent colds, 'pneumonia', infectious diseases of childhood, foreign bodies in the bronchus, and post-operative pulmonary infections.

Findlay and Delille (7), in 25 cases of bronchiectasis in children, found that in all but three cases the condition could be traced to some acute pulmonary disease, such as primary broncho-pneumonia or to broncho-pneumonia secondary to infectious fevers and pleurisy. The importance of acute infections, such as influenza, pertussis and measles as causative agents of bronchiectasis has also been stressed by Elliott (17) and Opie (18).

In the following table are summarized the findings in 65 cases of bronchiectasis which had reliable records of the mode of onset; of these 31 were investigated and diagnosed by lipiodol injection and 34 were examined at autopsy. Apart from three acute cases of bronchiectasis and one of congenital bronchiectasis, only 7 cases out of 65 cases had an insidious onset.

In many cases there was a history of recurring attacks of 'pneumonia', and some patients gave a history of yearly or even more frequent attacks; in 25 per cent. of cases the initial attack of pneumonia occurred during the first year of life and in another 35 per cent. of cases during the second year, so that unless all these cases are considered of congenital origin, it is safe to assume that pneumonia was actually the starting-point of the bronchiectasis, although later in life it may have been a manifestation of the disease.

TABLE IV

Mode of onset.	Lipiodol cases (31).	Autopsy cases (34).	Total (65).
'Pneumonia'	19	8	27
Whooping-cough	4	2	6
Bronchitis	2	12	14
Influenza	1	0	1
Abscess of lung	1	0	1
Empyema	1	0	1
Foreign body in bronchus	0	2	2
Gassing in the war	0	2	2
Acute	0	3	3
Congenital	0	1	1
Insidious	3	4	7

Although only one case in my series gave a definite history of influenzal infection, this type of infection is probably a common and important aetiological factor of bronchiectasis. The work of Blake and Cecil (19) on experimental pneumonia has shown that in the case of influenza bacillus pneumonia, the bacilli do not invade the lung proper to any extent but remain confined to the bronchial tree. The most striking feature of the experimentally produced disease is an intense inflammation of the trachea and of the bronchi. The epithelium is desquamated and the walls are thickened by inflammatory exudate. Pathological studies in man made during the last pandemic of influenza also showed that the pure form of influenza-pneumonia was characterized by a tracheo-bronchitis with inter-

stitial pneumonia, alveolar emphysema, haemorrhagic oedema, and hyaline deposits within the alveoli and the terminal bronchioles. The muscular layers of the bronchioles showed marked degeneration and atrophy resulting in weakening of the bronchial wall with a tendency to dilatation and bronchiectasis (20). In addition to pneumococcal, streptococcal, and influenzal infections, there may be other organisms responsible for the weakening of the bronchial wall. Spirilla and fusiform bacilli have been repeatedly found in idiopathic bronchiectasis as well as in the secondary form (Pilot and Davis (21)). Although these organisms are normally saprophytic inhabitants of the mouth, they may become pathogenic, and it has been suggested that they may be partly responsible for the weakening of the bronchial wall, just as the *Spirochaeta pallida* is responsible for the weakening of the wall of the aorta which leads to aneurysm (20).

Another very important source of infection in bronchiectasis is accessory + nasal sinus disease. I have, in collaboration with Mr. A. D. Sharp, investigated sixteen cases of bronchiectasis from this point of view. Twelve of these cases had been investigated by a lipiodol injection, while the remainder had been diagnosed clinically and by ordinary radiological examination. In thirteen out of sixteen cases definite sinus infection was found to be present, while another case had septic tonsils.

Rist (22) has been very insistent in demonstrating the association between chronic coughs and sinusitis, and the aetiological role which sinusitis plays in bronchiectasis has been stressed by Mullin, Webb, Adam, and Brown (23).

Dennis (24), out of sixty patients with nasal accessory sinus disease, found that twenty-four had bronchiectasis and twenty-eight suffered from asthma. There is also of course the possibility that the nasal sinuses may become secondarily infected by secretions from the lung during the act of coughing, but it is far more likely that nasal infection occurs first and that the lung becomes secondarily infected by the constant discharge downward of septic material from the nose.

To sum up, one may say that, attractive as the mechanical theories may be, it would appear that infection alone is able to account for bronchial dilatation without any additional factors such as distension of the tubes from within or traction upon the tubes from without. Infection of the bronchi may be the result often of an attack of pneumonia early in life, may follow infectious diseases of childhood such as measles, whooping-cough, or may be secondary to a nasal infection. This is also borne out by the fact that bronchiectasis is very often a disease of the very young; thus in sixty cases considered here the condition was present during the first five years of life in 50 per cent. of cases. Although the adult type of bronchiectasis may be compatible with a fairly long life and not much impairment of health, the disease in childhood has a very high mortality; in a series of forty-one autopsy cases in which death had been due to bronchiectasis, 50 per cent. died before puberty, with the highest mortality during the first five years of life, and nearly two-thirds of the cases died

before they were 30 years of age. The most frequent causes of death were broncho-pneumonia, empyema, and pyo-pneumothorax, while gangrene of the lung, fatal haemoptysis, and abscess of the brain were the exception. The following table summarizes the causes of death in fifty-five cases observed at autopsy.

TABLE V

Cause of death.	No. of cases.
Broncho-pneumonia	16
Empyema	10
Pyo-pneumothorax	3
Lung abscess	1
Gangrene of lung	2
Fatal haemoptysis	1
Abscess of brain	3
Cardiac failure	4
Nephritis	1
Total deaths from bronchiectasis	41 (74.5 %)
Death from other causes	14 (25.5 %)

Summary

1. Bronchiectasis is far from being an unfrequent disease, and is probably one of the commonest types of respiratory disease.

2. Bronchiectasis often begins as a unilateral affection and only later tends to become bilateral. This is suggested by a comparison between clinical and autopsy cases.

3. Different types of bronchial dilatation, as revealed after a lipiodol injection, have been described and their relative frequency noted.

4. The pathogenesis of bronchiectasis has been discussed; although the mechanical theories cannot be altogether excluded, it would appear that infection is the most important factor.

5. This conclusion has been reached from a consideration of analogous dilatations occurring in the salivary glands; further support is afforded by the frequent history of some respiratory infection such as broncho-pneumonia, measles, pertussis, and influenza anteceding bronchiectasis, and by the high incidence of accessory nasal sinus infection in this disease.

6. Bronchiectasis is primarily a disease of the young; thus in 50 per cent. of the cases considered here the condition was present during the first five years of life.

7. A review of fifty-five autopsy cases showed that death was caused directly or indirectly by the bronchiectasis in 74.5 per cent. of cases.

8. The highest mortality occurred during the first five years of life, and nearly two-thirds of the patients died before reaching the fourth decade.

I wish to thank the Physicians of the General Infirmary at Leeds for allowing me to refer to patients under their care.

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FIG. 1. Bilateral tubular bronchiectasis

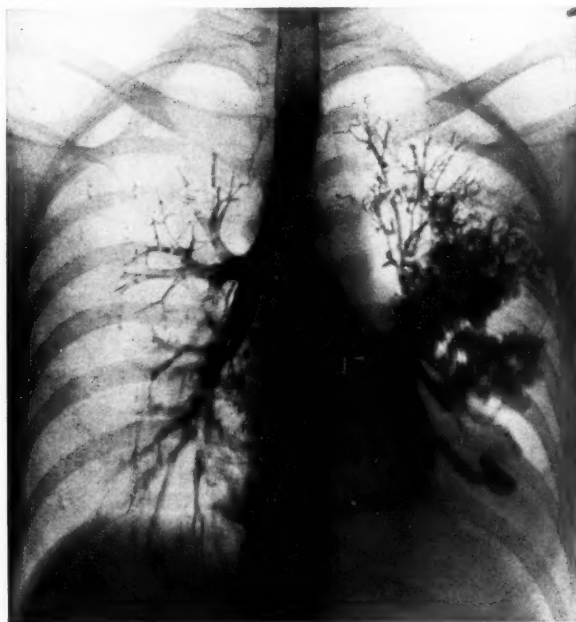


FIG. 2. Atelectatic fusiform bronchiectasis



FIG. 3. Saccular bronchiectasis

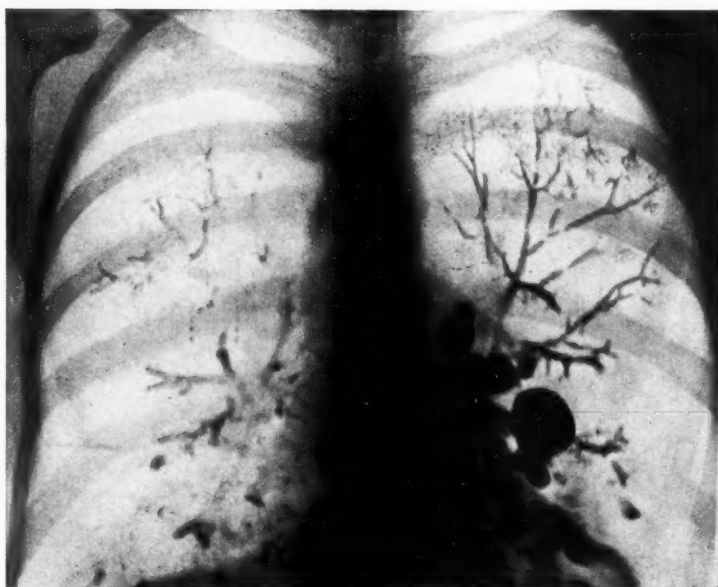


FIG. 4. Marked saccular bronchiectasis

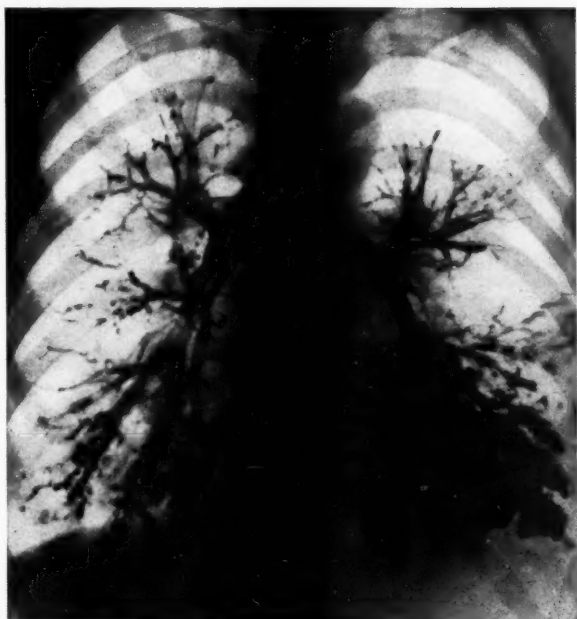


FIG. 5. Saccular bronchiectasis (Lt) and intermediate form between tubular and saccular (Rt)



FIG. 6. Bilateral moniliform bronchiectasis



FIG. 7. Atelectatic bronchiectasis with triangular shadow

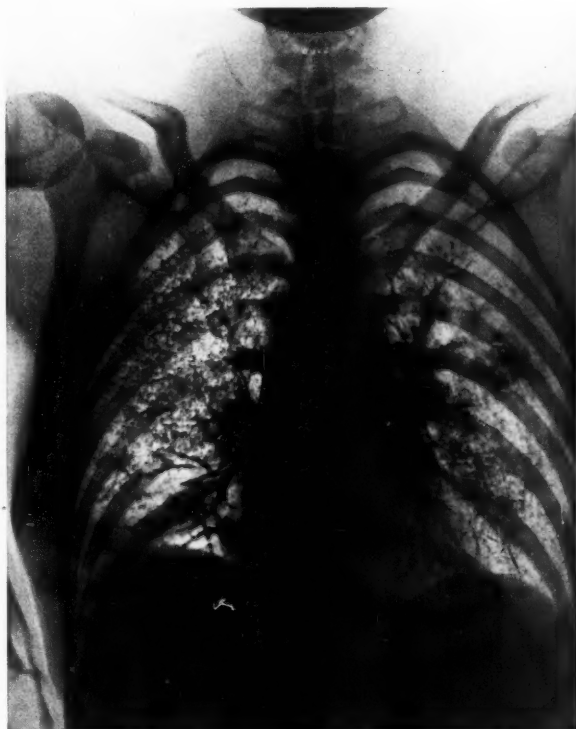
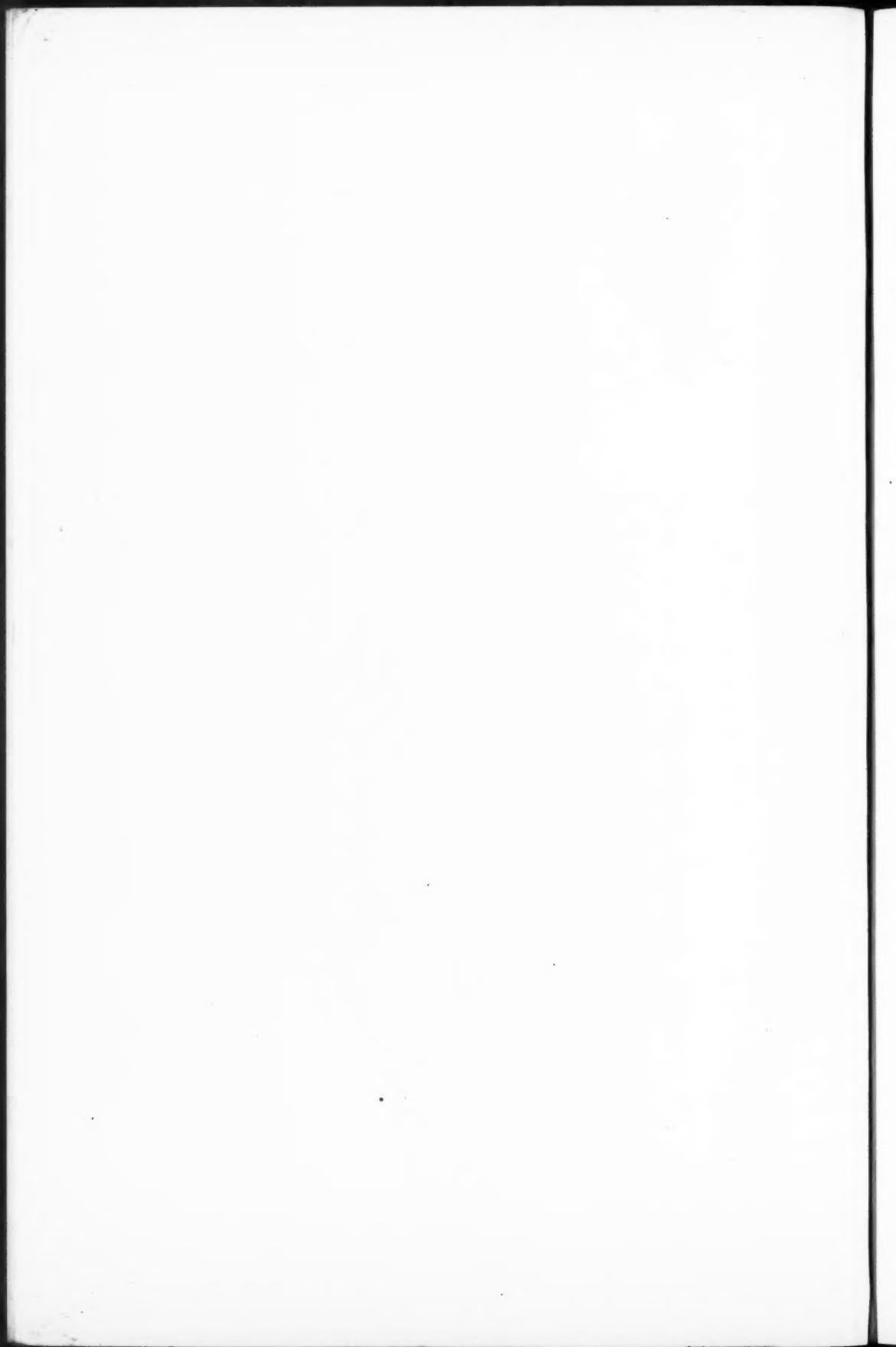


FIG. 8. Early and localized bronchiectasis cured by artificial pneumothorax treatment



OSTEITIS DEFORMANS¹

BY T. J. O'REILLY AND JOSEPH RACE

(From the Devonshire Hospital for Rheumatic Diseases, Buxton)

With Plates 29 to 32

Introduction

THE credit for describing this disease as an entity is due to Sir James Paget (1) who, in 1876, presented to the Medico-Chirurgical Society of London a paper on a form of chronic inflammation of the bones with a report of five cases. He named the condition 'after its most striking character, osteitis deformans'.

In 1869 Wilks (2), who had made a careful study of a case of this disease, published it with post-mortem notes in the *Transactions of the Pathological Society of London* as a case of osteoporosis, or spongy hypertrophy of the bones, and this case was included in Paget's collection.

In a second communication on this disease in 1882, Paget (3) noted that Czerny in 1873 had applied the name osteitis deformans to 'a rare acute inflammation of the lower part of the tibia and fibula inducing softening and angular bending and followed by hardening'.

Even earlier observers had noted cases of the disease described by Paget: in 1697 Malpighi, in his *opera posthuma*, called attention to diffuse hypertrophy of the skull, a condition later studied by Virchow under the name of 'leontiasis ossa' and believed to represent a partially developed form of osteitis deformans; Saucerotte (4) in 1801 and Rullier (5) in 1812 also reported cases.

During the thirteen years following the publication of his original paper Paget saw eighteen additional cases, making a total of twenty-three cases observed by him up to the year 1889. Paget apparently regarded the disease as of recent origin, but Knaggs (6) has noted old museum specimens which show that it had attracted attention long before, and cites a typical skull included in John Hunter's collection and dug up in the Stepney Parish churchyard in the eighteenth century.

Occasional cases continued to be recorded, and in the *Transactions of the Medical Society of London* from 1881 to 1918 seven cases are reported, usually because of some anomalous feature. In the *Transactions of the*

¹ Received April 1, 1932.

Clinical Society of London between 1868 and 1904, fourteen cases are recorded.

In 1901 Packard, Steele, and Kirkbride (7) made a careful study of the cases reported to that date and found sixty-six typical examples of the disease. To this number they added one case of their own.

Higbee and Ellis (8) again reviewed the literature in 1910 and estimated that there were 158 cases on record.

In 1914 Da Costa and co-workers (9) reviewed the literature since this last study and found fifty additional cases to which they added three cases personally observed and the histories of two others, making a total of 213 reported cases up to that date.

Clinical Features

Age incidence. The disease rarely begins before 40, and in fifty-one cases studied by Packard, Steele, and Kirkbride (7) the average age of onset was 49 years. Much earlier onsets have been reported: 21 years, Moizard and Bourges (10); 16 years, Sonnenberg (11); 12 years, Elsner (12); 16 years, Jones (13); 13 years, Thibiérge (14); 14 years, Hartman (15); 8 years, Da Costa (9); and one aged 35 whose head had been large from birth by Klestadt (16). The oldest age of onset recorded is 79 (7), and the longest duration was in a patient of Moizard and Bourges (10) in whom the disease lasted fifty-two years.

The present communication is a study of cases met with among the ordinary admissions to the Devonshire Hospital for Rheumatic Diseases, Buxton, during 1930-1, and in Table I we have arranged these thirty cases in the order of their ages and also in the order of the calculated age of onset of the disease.

TABLE I

Age when observed.			Age at onset.		
Decade.	Cases.	%	Decade.	Cases.	%
35-45	0	Nil	35-45	3	10
45-55	11	37	45-55	15	50
55-65	18	60	55-65	12	40
65-75	1	3	65-75	0	Nil
Earliest.	46 yrs.		Earliest.	43 yrs.	

The date of onset is only an approximate one, probably always on the high side, depending as it does on the patient's observations and the severity of his symptoms.

We believe that early cases of Paget's disease, though rare, do occur, but we are not altogether satisfied that some of the early cases recorded in the literature are not cases of generalized fibrocystic disease.

Sex. The following figures have been recorded by the undermentioned observers :

	Male.	Female.
Packard, Steele, and Kirkbride (7)	41	24
Da Costa (9)	0	3
Lasch (17)	3	2
Kay (18)	13	8
Hunter (19)	4	3
Present series	24	6

Whatever may be the value of the figures of other observers on the relative sex incidence, we are convinced that our own bear no relation to it. Most of our cases were detected through radiograms and the sex incidence in our series will therefore be materially affected by the relative numbers of males and females radiographed. The total radiograms of males were far in excess of those of females and consequently invalidate our figures.

Heredity. Da Costa and co-workers (9) made a study of the influence of heredity in this disease and collected a number of instances of family involvement from the literature: a father and two sons (Oetlinger and Agasse-La Font, 20); two brothers (Manwaring-White, 21); two brothers (Lunn, 22); mother and son (Higbee and Ellis, 8); mother and son (Berger, 23); sister and brother (Kilner, 24); sister and brother (Walter, 25); father and daughter (Pick, 26); two members of a family (Robinson, 27); mother and son (Hurwitz, 28); two sisters (Parry, 29); two brothers (Abbé, 30); two sisters (Da Costa, 9).

They calculated that on the total number of cases recorded to that date (1915) a family involvement existed in 7 per cent. It is difficult to estimate the influence of heredity as family histories are very incomplete. We were unable to trace family involvement in any of our cases.

Incidence. All the figures relating to the incidence of this disease are unsatisfactory. Hurwitz (28) found only three cases in over 30,000 admissions to the Johns Hopkins Hospital. In over 38,000 admissions to the New Jefferson Hospital (9), during a period of seven years, there were only three cases of osteitis deformans.

By courtesy of the Medical Registrars of the London Hospital and the Leeds General Infirmary, and of the Superintendent of Guy's Hospital, we have obtained the following figures for the admission of cases of Paget's disease during recent years.

Guy's Hospital, London. In the orthopaedic department there were fifty cases during the last three years in a total of about 6,600 cases.

General Infirmary, Leeds, during the three years 1927-30, had eleven cases in a total of 42,000 in-patients.

London Hospital, during the three years 1926-9, had ten cases out of 14,100 total medical admissions. During 1930-1, when bone dystrophies were under investigation, out of a total of 8,000 admissions there were thirty-one cases of Paget's disease.

During a period of eighteen months, among 5,000 admissions to the Devonshire Hospital for Rheumatic Diseases, we have collected thirty cases, and this number is probably incomplete. While we claim no accuracy for the disease incidence based on these figures, we think we are justified in regarding the disease as more prevalent than is usually supposed.

Physical features. Sir James Paget's original account (1) of this disease leaves little for addition or correction: 'The disease begins in middle life or later, is very slow in progress, may continue for many years without influence on the general health, and may give no other trouble than those which are due to the changes in shape, size, and direction of the diseased bones. Even when the skull is largely thickened and all its bones exceedingly altered in structure the mind remains unaffected. The disease affects most frequently the long bones of the lower extremities and the skull, and is usually symmetrical. The bones enlarge and soften, and those bearing weight yield and become unnaturally curved and mis-shapen. The spine, whether by yielding to the weight of the overgrown skull or by change in its own structures, may sink and seem to shorten with greatly increased dorsal and lumbar curves; the pelvis may become wide; the necks of the femora may become nearly horizontal; but the limbs, however misshapen, remain strong and fit to support the trunk.

'In its earlier periods and sometimes through all its course the disease is attended with pains in the affected bones, pains widely various in severity and mainly described as rheumatic, gouty, or neuralgic, not especially nocturnal or periodical. It is not attended with fever. No characteristic conditions of urine or faeces have been found in it. It is not associated with syphilis or any other known constitutional disease unless it be cancer.'

Clinically the disease is characterized by thickening, bending, and elongation of bone, with or without pain. We believe the pain to be due to a strain placed on the other supporting tissues by the failure of the softened bone to fulfil its normal supporting function.

The presence of pain, and its severity and periodicity, will depend therefore on the part of the skeleton affected and on the rapidity and extent of the bone changes. Whether the morbid process in the bone may itself be a primary cause of pain, we have not been able to determine. It is difficult in any instance to eliminate the factor of strain; and in favour of the contrary view we may state that eight (27 per cent.) of our patients who were without physical signs but with well-marked X-ray and biochemical findings had experienced no pain from the disease.

Our cases may be divided into three clinical groups:

- I. Those showing physical signs of osteitis deformans.
- II. Those without physical signs but with symptoms due to the osteitis deformans.
- III. Those without physical signs or symptoms of osteitis deformans.

Twelve (40 per cent.) of the thirty cases that we have studied belonged to the first group showing thickening, bending, and elongation of bone with

the subsequent deformities described by Paget. All of them had symptoms proceeding from these lesions and the diagnosis presented little difficulty.

Ten (33 per cent.) of the cases belonged to the second group with symptoms due to the osteitis deformans but without physical signs. They were clinically the most interesting cases. All of these patients complained of a dull aching pain in the lumbar region of the back, hips, and thighs, of very gradual onset, and slowly increasing in intensity and area. The pain was brought on and intensified by anything which induced a strain in the affected part; always by prolonged standing or bending and occasionally when sitting or lying in bed. It was usually eased by removal of the strain, and some patients found that this could be done when standing or sitting by pressing the back against a firm surface: a small pillow placed under the lumbar spine relieved the pain when lying.

TABLE II

Cases with physical signs of osteitis deformans.			Cases without physical signs but with symptoms due to osteitis deformans.			Cases without signs or symptoms of osteitis deformans.		
Name.	Age.	Duration.	Name.	Age.	Duration.	Name.	Age.	Duration.
S. J. B.	66	9 yrs.	J. C. B.	63	10 yrs.	D. D.	63	?
O. T.	65	19 "	J. Mn.	62	2 "	J. J.	62	?
E. B.	65	14 "	J. Me.	61	3 "	W. H.	62	?
J. H.	65	12 "	A. M. S.	61	2 "	C. H.	58	?
M. H.	61	6 "	W. B.	56	2 "	J. McK.	52	?
A. M.	58	2 "	S. H.	56	2 "	J. T.	52	?
W. W.	57	6 "	J. H. W.	56	1 "	T. G.	49	?
H. E. G.	57	2 "	T. H.	53	8 "	J. G.	46	?
W. H. S.	55	8 "	G. A. G.	53	5 "			
T. C.	55	4 "	J. W. B.	48	3 "			
J. K.	52	4 "						
S. W.	46	3 "						

The diagnosis of osteo-arthritis of the hips or lumbar spine is suggested, but the symptoms in these conditions are usually more clearly defined.

The third group comprised eight cases (27 per cent.) and the diagnosis was an accidental one made during an X-ray examination for some other possible condition.

Six of our patients complained of attacks of heat and profuse sweating in the face, front of the head, and chest, brought on by very moderate exertion; the areas usually corresponding to the spinal involvement. We attribute this symptom to a secondary disturbance of the vegetative nervous system.

In Table II we have arranged the cases in the three clinical groups with the age and duration of the disease. It will be noticed that the age-span in each group is approximately equal, and that the progress of the disease as measured by the onset of bone deformity is by no means proportional to the duration; there are several high figures in the second group and some low ones in the first.

Radiographic appearances. The diagnosis of osteitis deformans in a great

proportion of the cases was made on an X-ray examination in which the appearances were usually conclusive, but those that were dubious were considered in conjunction with the biochemical findings before making a definite diagnosis.

TABLE III

Frequency of Involvement of Various Bones in 30 Cases

Pelvis	26	Left fibula	5
Lumbar spine	24	Right clavicle	3
Left femur	16	Right fibula	2
Right femur	16	Left clavicle	2
Spine	15	Left humerus	1
Left tibia	10	Scapula	1
Right tibia	8	Right radius	1
Skull	8		

Léri (31) has emphasized a 'cotton-wool' appearance of the bones as diagnostic of this disease, an observation previously made by Léri and Londe and especially well described by Hudelo and Heitz (32). This, although it appears at some time in almost all the bones affected, is not the first change or the only one to be seen in them.

The texture of the bones in this disease shows three changes in the radiograms, of which any one or more may modify the bone separately, especially in the early stage, and a combination of which produces the classic radiographic appearance of the disease.

Usually, the earliest of these changes is a coarsening of the bone appearance due to a decalcification which accentuates the normal bone lines and produces an appearance of simplification of the normal bone structure. This is most often seen in the pelvis and vertebrae.

The second change, which is usually the characteristic one of the vault of the skull, is a complete loss of the normal sharp texture of the bone and its outline, so that the appearance becomes hazy and looks as though seen through ground glass.

The third change, generally a sequel to one of the preceding, is a deposition of amorphous calcium salts which spreads throughout the bone like a white steamy cloud and, becoming dense, obliterates all detail in the radiograms.

The X-ray appearances throughout the affected parts of the skeleton have much in common, but will vary with the previous structure of the diseased bones and the stage to which the disease has progressed. Even in the same bone varying appearances may be noted, probably due to the intensity and duration of the disease process. The three stages that we have differentiated above are descriptive ones only and have no necessary sequence or independent existence in time.

For descriptive purposes we have divided the skeleton into (1) the long bones, (2) the flat bones, and (3) the skull. In the long bones there is firstly an increase in thickness of a part of the shaft with a haziness of outline of the boundary between this part of the shaft and the soft tissues; and a

TABLE IV
Area of Bone Involvement

Name.	Skull.	Spine.	Lumbar spine.	Pelvis.	Right femur.	Left femur.	Right tibia.	Left tibia.	Right fibula.	Left fibula.	Right clavicle.	Left clavicle.	Left humerus.	Scapula.	Total number of bones involved.
O. T.	+	+	+	+	+	+	+	+	+	+	+				11
J. K.	+	+	+	+	+	+	+	+	+	+		+			10
G. A. G.	+	+	+	+	+	+	+	+	+	+					9
J. H.	+	+	+	+	+	+	+	+							8
A. M.	+	+	+	+	+	+	+	+							8
E. B.	+	+	+	+	+	+	+	+							8
W. B.	+	+	+	+	+	+	+	+					+		9
C. H.	+	+	+	+	+	+	+				+				8
W. W.	+	+	+	+	+	+	+	+		+					6
J. W. B.	+	+	+	+	+	+	+	+		+					6
S. J. B.	+	+	+	+	+	+	+	+							5
M. H.	+	+	+	+	+	+	+	+							5
J. C. B.	+	+	+	+	+	+	+	+							5
J. G.	+	+	+	+	+	+	+	+							5
T. G.	+	+	+	+	+	+	+	+							4
S. H.	+	+	+	+	+	+	+	+							4
H. E. G.	+	+	+	+	+	+	+		+						4
J. Me.	+	+	+	+	+	+	+								3
W. H.	+	+	+	+	+	+	+								3
D. D.	+	+	+	+	+	+	+								3
S. W.	+	+	+	+	+	+	+								3
W. H. S.	+	+	+	+	+	+	+		+						3
T. H.	+	+	+	+	+	+	+								2
J. H. W.	+	+	+	+	+	+	+								2
A. M. S.	+	+	+	+	+	+	+								2
J. Mn.	+	+	+	+	+	+	+								2
T. C.	+	+	+	+	+	+	+								2
J. J.	+	+	+	+	+	+	+								2
J. H. McK.	+	+	+	+	+	+	+								1
J. T.	+	+	+	+	+	+	+				+				1

coarsening of the bone structures due to an irregular decalcification which accentuates the bone lines in the long axis. Bending, increase in thickness with occasional loss of texture and clouding occur, and later the cortex becomes dense. Small clear areas are sometimes observed in the dense and thickened bone (Plate 29, Figs. 1 and 2).

In the flat bones, of which the pelvis shows the changes most clearly, the first change that we have detected is a decalcification which is not uniform but occurs in such a way as to give the bone a coarsened appearance and to accentuate occasional bone lines which stream across the sacrum and the iliac crests. An increase of density occurs along the pelvic brim and spreads out like a white cloud through the bone. Occasionally only one side of the pelvis is affected, or different appearances may be contrasted in the two sides (Plate 31, Fig. 4, Plate 32, Fig. 5).

In the skull the earliest observable changes are a haziness and loss of bone outline in the vault followed by a replacement of the normal bone texture by a cotton-wool appearance, and an increase in thickness of the bone, on which are scattered small woolly flocks. In this Pagetized bone, areas often appear varying in size from a pea to a bean, circular or oval in outline, and consisting of a central piece of woolly bone surrounded by a sharply defined clear circle in which marked decalcification has taken place. A number of these may be found scattered over the vault, and are probably identical with the areas described by Schüller (33) under the term 'osteoporosis circumscripta' and later regarded by Weiss (34) as unusual but typical manifestations of Paget's disease. The bones become markedly thickened and show great irregularity in their calcification. The base of the skull shares in the changes, and all the bones become progressively denser (Plate 30, Fig. 3).

The sella turcica is usually normal in appearance. In the later stages of the disease the sphenoid becomes thickened, and in one of our patients there appears to be an encroachment on the fossa with consequent narrowing, but no special symptoms suggesting pituitary disturbance were present.

In one case only an abnormally small fossa was noted in bone still uninvolved. The patient was a female (aged 35) and showed lack of genital development.

Attention was drawn by Da Costa and co-workers (9) to calcification of the pineal body in a patient under their observation. We have noted its occurrence in six of our cases out of eleven skulls in which a satisfactory search could be made for it.

We have attempted to correlate the radiographic appearances with the pathology at the end of that section.

Present concurrent disease and focal sepsis. In an endeavour to assess the value of the Suspension Stability results and the blood picture, the presence of concurrent disease and focal sepsis requires consideration.

We have arranged the incidence of these in Table V.

TABLE V

Present concurrent disease.		Focal sepsis.	
Slight fibrositis	7	Chronic tonsillitis	7
Well-marked fibrositis	3	Gingivitis	5
Infective arthritis	1	Gingivitis and septic stumps	2
<i>B. coli</i> cystitis	1	Pyorrhoea	1
Hyperthyroidism	1	Chronic cholecystitis	2

Seven patients were free from both concurrent disease and septic foci, and in all of these the Suspension Stability results were normal.

Cardiovascular. In Table VI we have arranged our cases in the order of their systolic blood-pressures. We have noted calcification of the arteries and its degree, when present in the radiograms, and the condition of the superficial arteries.

TABLE VI
Cardiovascular System

Name.	Age.	Duration.	B.-P	Calcification.	Condition of superficial arteries.
A. M. S.	61	2 yrs.	216/96	0	Slightly thickened
J. H.	65	12 "	210/130	—	Thickened
H. E. G.	57	6 "	184/96	0	Thickened and slightly tortuous
S. W.	46	3 "	182/106	0	Slightly thickened
J. J.	62	?	176/102	+++	Much thickened and tortuous
J. W. B.	48	3 "	168/90	0	Thickened and slightly tortuous
S. J. B.	66	9 "	160/70	0	Slightly thickened and slightly tortuous
J. H. W.	56	1 "	158/86	0	Much thickened and slightly tortuous
O. T.	65	19 "	152/84	+	Much thickened; tortuous; calcified
S. H.	56	2 "	152/78	0	Slightly thickened
T. H.	53	8 "	150/88	0	Slightly thickened and slightly tortuous
G. A. G.	53	5 "	148/86	+++	Normal
J. Me.	61	2 "	144/78	+	Normal
C. H.	58	?	142/70	+	Normal
J. Mn.	62	2 "	142/86	0	Slightly thickened
E. B.	65	14 "	140/80	+++	Thickened; calcified; (frequent extrasystoles)
T. C.	55	8 "	136/74	0	Slightly thickened
J. C. B.	63	10 "	138/65	+	Normal
J. G.	46	?	136/78	++	Thickened and slightly tortuous
A. H.	61	?	130/75	—	—
M. J. W.	58	?	120/65	—	—
J. H. McK.	52	1 "	110/76	0	Normal

+ = present; 0 = absent; — = not examined.

It will be seen that seven out of the twenty-two cases recorded have a systolic blood-pressure over 160 mm.: a finding probably not abnormal for the age-span of the group. The figures bear no relation to the age of the patient or to the duration of the disease.

Calcification of the arteries was present in twelve (43 per cent.) out of the twenty-eight cases in which a satisfactory search could be made for it in the radiograms. It bears no relation to any of the other findings, and we suggest that its frequency and intensity may possibly be due to the excess of phosphoric esterase in the blood and which, although probably unable to initiate, accelerates and intensifies the deposition of calcium salts in degenerating vessels.

Mitral incompetence of a minor degree was present in two patients, one of whom also had a soft systolic murmur in the aortic area. One patient had evidence of considerable myocardial degeneration.

Gastro-intestinal. Except for the probable complication of chronic cholecystitis in three cases, we found no evidence of disease of the gastro-intestinal system in any of our patients. A macroscopic and microscopic examination of the faeces in a few cases revealed no abnormality and this line of investigation was not pursued farther.

Thirteen cases were examined by the usual fractional test meal with the results given in Table VII in which are also included some figures obtained from healthy persons in the later decades of life by Davies and James (35).

TABLE VII

Cases.	Osteitis deformans.	Davies and James, persons 60-95 yrs.
	13	100
Achlorhydria	23 %	32 %
Hypochlorhydria	23 %	12 %
Normal	46 %	43 %
Hyperchlorhydria	8 %	13 %

Compared with healthy young people, our cases show an excessive percentage with achlorhydria, but there is no significant variation, considering the size of the series, from those found by Davies and James.

Pathology

Enlargement and softening characterize the bones affected by this disease. This result is due to the complete or almost complete removal of the original osseous tissue and its replacement by new bone formed on a different plan and in a larger mould. The change is produced by a highly vascular young connective tissue which permeates the bone from the medulla to the under-surface of the periosteum with which it blends.

This new tissue has osteogenic properties, and as the original bone disappears new bone formation begins in it, so that the two processes, absorption and ossification, proceed simultaneously. The proliferating soft tissue forms first and slowly expands the periosteal envelope as it absorbs the original bone; and later new bone is formed in this tissue. Thus in the early stage of the disease the bones are soft and vascular and undergo the various deformities which characterize the disease clinically; later they become hard and dense.

We have not had an opportunity of making a satisfactory histological examination of the bones in this disease and, owing to the confusion of osteitis deformans and osteitis fibrosa in the past, very little reliable information is available. The recent description by Donaldson (36) which we have summarized below seems to us to be the most satisfactory.

The initial lesion appears to be one which affects the bone corpuscles. As a result the lime salts begin to disappear from the surrounding lamellae; osteoclasts appear, and a progressive decalcification takes place. Accompanying and following this a very active proliferation of cells takes place with the formation of many new capillary blood-vessels so that the gradually enlarging cancellous spaces and Haversian canals become filled with a highly cellular and richly vascular tissue. These proliferating cells revert to a more or less embryonic undifferentiated type apparently identical with mesenchyme cells, and multinucleated giant cells appear which function as osteoclasts. Fibrils commence to appear among the undifferentiated cells and a fibro-cellular tissue is formed. These fibrils become thickened, swollen, and fused, forming an osseo-mucinous matrix in which the cells become embedded, and the irregular trabeculae formed in this way become linked up with one another so that a network of 'osteoid tissue' appears in the fibro-cellular matrix.

Lime salts are deposited in the 'osteoid tissue' which becomes calcified. Osteoblasts form layers of osseo-mucin on the sides of this calcified scaffolding in which they become embedded. These layers gradually become calcified, and in this way an excess of reticular spongy bone is formed so that the affected bones become thicker than before.

When the radiograms are considered in terms of the pathological changes it seems probable that the early decalcified appearance with accentuation of the bone lines is due to the permeation of the Haversian canals by the new connective tissue causing a decalcification and accentuating some intervening lamellae which remain unaffected. Activity of the bone corpuscles and permeation of canaliculi would give rise to the haziness and cotton-wool appearance; and the deposition of calcium salts in the new osteogenic tissue be responsible for the amorphous cloud-like appearance and the subsequent increase in density; the relative sequence and degree of the changes being responsible for the varying appearance of the radiograms.

Complications

Paget (3) noted that 'this disease (osteitis deformans) has appeared in no usual relation whether by inheritance or coincidence with any other disease except gout'.

Duckworth (37) quotes a case of a clergyman, with a history of gout in his maternal grandfather, who had Paget's disease in both tibiae, and who at the age of 60 developed typical attacks of acute gout in his joints and tophi in his ears.

One patient only in our series had a history suggesting gout. Tophi were absent, but his blood uric acid was 4.7 mg. per cent. We estimated the blood uric acid by the Benedict direct method in eight of our cases with the following results: 4.7, 4.6, 4.0, 4.0, 3.9, 3.6, 3.5, 3.1. (Normal maximum 4.5.) Normal results for the blood uric acid are also reported by Lasch (17).

The frequency with which *malignant disease* terminated the lives of his patients impressed Paget: in eight cases whom he traced to the end, three died of sarcoma, one twenty-two years after the onset of the disease.

Packard, Steele, and Kirkbride (7) in sixty-six cases found only eight with malignant disease, whilst Grüner, Scrimger, and Foster (38) stated that up to 1902 only fourteen of the recorded cases were associated with malignant disease. Higbee and Ellis (39) found only two benign tumours in the cases reported between 1902 and 1911.

Knaggs (6), in a very complete study of the disease in 1926, expressed the opinion that the frequency of this complication had been accidentally exaggerated. Hartfall (40) observed eighteen cases over a period of ten years, and found that three developed sarcoma. Coley and Sharp (41), in seventy-one cases of osteogenic sarcoma in patients over 50 years of age, found that twenty (28 per cent.) of the cases were associated with osteitis deformans.

Fractures of the diseased bones are an occasional occurrence, especially when the bone is in the decalcifying stage. In eighteen cases under observation at the Leeds Royal Infirmary for a period of ten years, in all of whom the skull was involved, four fractures occurred (Hartfall, 40). One of our patients had a fracture through the neck of the femur on admission.

The fractures unite as readily as those in normal bone. Knaggs (6), Morris (42).

Ulceration of the skin over a deformed tibia with infection and sinus formation in the diseased bone has been described, and was ascribed to impaired nutrition of the skin with local injury.

The changes in shape and thickening of the skull and vertebral column occasionally give rise to lesions of the nervous system. Headache was present in five of our patients, in all of whom the skull was involved, and may be due to strain on the dura mater caused by the altering shape of the skull. We have already mentioned the attacks of sweating, which we attribute to a secondary disturbance of the vegetative nervous system. Symptoms due to cranial nerve involvement are uncommon: Wyllie (43), commenting on this phase, reported two cases in which the skull was involved with optic atrophy due to compression of the nerves at the optic foramen; Gregg (44) reported compression of the cranial nerves causing neuralgia, paralysis, and disturbances of the special senses; Jenkins (45) discussed deafness in patients with osteitis deformans and concluded that it was secondary to involvement of the skull bones. Progressive deafness with tinnitus was present in two of our patients, both of whom had an extensive involvement of the skull. Compression of the cord with resulting paraplegia has been reported in three cases (43) and may occur in two ways: either the marked softening and increase in thickness of the vertebrae, which occur in some cases, may produce sufficient narrowing of the vertebral canal to cause compression, or localized pressure points may arise from the formation of osseous excrescences on the thickened vertebrae. The symptoms were relieved in two of the three cases by laminectomy.

The absence of mental symptoms was commented upon by Paget in his account of the disease. Cases of altered mentality and true psychoses in

association with osteitis deformans have been recorded by Hann (46), Smith (47), and Kaufman (48), but in most of these the aetiological relationship of the mental changes to the osteitis deformans is extremely doubtful. Hartfall (40), in 1931, reviewed the literature on this subject and noted that in the eighteen cases of the disease with involvement of the skull under his observation for ten years none showed any sign of mental change. None of our cases displayed any mental alteration and the apparent dullness and reticence in one patient was explained by the increasing deafness and tinnitus from which she suffered.

Osteo-arthritis of both hips was present in three of our cases and of the right hip alone in one case. The signs of this condition may be simulated by a shortening and bending of the neck of the femur with increase in size of the great trochanter.

Aetiology

Many and diverse hypotheses have been suggested regarding the aetiology of this disease, but up to the present none has met with general acceptance.

Paget thought that the disease was of an inflammatory nature and distinguished it from the other known causes of bone inflammation and hypertrophy.

Hutchinson (49) believed that the disease was 'simply an infective osteitis begun in consequence of a contusion in one bone and spread by infection to the others'.

Oetlinger and Agasse-La Font (20) attributed the disease to intoxication by mineral acids due to the chlorine-laden atmosphere in which several of their patients worked.

Lancereaux (50) considered that the nervous system produced the bone changes, and Pitres and Vaillard (51) were of the opinion that the lesion was a degeneration of the nerves at the nutrient foramina.

Gilles de la Tourette and Marinesco (52), who found lesions in the medulla, thought that the bone changes were trophic, and Prince (53) compared the disease to the myopathies of spinal origin.

Kleppel and Weil (54) reported a case with unilateral involvement of the skeleton and local hyperthermia suggesting a nervous lesion.

The nervous lesions are not constant; are generally absent; and when present may be secondary or due to some concurrent disease. Léri (31), in a study of the question in 1926, concluded that while not entirely eliminating the possibility of a nervous lesion, no aetiological relationship had been demonstrated.

Lannelongue (55), and Fournier (56), in 1903, put forward the hypothesis that the disease was a late manifestation of hereditary syphilis, and Ménétrier and Gauckler (57) regarded not only hereditary, but also acquired syphilis, as a causative factor; that the disease is a parasymphilitic affection.

Da Costa and co-workers (9), in 1914, collected the reports of the Wasser-

mann reaction in thirty-four cases and found seven positive results and twenty-seven negative ones. Léri (31), in 1924, collected similar reports in fifty-six cases which gave sixteen positive and forty negative results.

The conclusion of Léri was : ' En somme s'il est très vrai que des pagétiques paraissent être parfois des syphilitiques héréditaires ou acquis, il ne nous paraît pas démontré, jusqu'à nouvel ordre, qu'il en soit toujours ainsi et moins encore que la maladie de Paget soit d'essence et de nature syphilitique.'

The Wassermann reaction was negative in every one of the eight of our cases that were tested, and we found no evidence of syphilis in any of our patients.

We entirely concur with the opinion expressed by Elsner (12) and von Kutscha (58) that no uncomplicated case of Paget's disease has given a positive Wassermann reaction.

Bacteriological studies by Ellis (9) and Levin (59) of pieces of excised bone were negative and failed to confirm the claim of the Italian observers, Morpurgo, Archangelli, and Fiocco of a causative diplococcus isolated from the bone.

A lesion of the arteries, either an arteritis or an arteriosclerosis, is regarded by Léri as producing the bone changes. Osteitis deformans then becomes a syndrome, the arterial lesions resulting from diverse causes : syphilitic, tuberculous, toxic, &c. This vascular hypothesis is dealt with in detail by Léri (31).

We have already dealt with the vascular findings under that heading and do not consider that they are consistent with this view.

That the disease is due to the loss or perversion of some internal secretion was suggested by Labadie-Lagrave (60) in 1893, and more recently found support from Da Costa and co-workers (9). These authors are inclined to implicate the pineal body, which they found calcified in an early case. We have noted this finding in our cases, and have commented elsewhere on the subject of calcification in the tissues of these patients. Experimental removal of the gland in rabbits by Exner and Boese (61) gave negative results and, so far as we are aware, no case of tumour of this body in the human subject has been associated with bone changes either before or after its removal.

The close relationship of parathyroid tumour to generalized fibrocystic disease suggests an analogy, and this disease has been frequently confused with osteitis deformans by pathologists, the two being classified under the common designation of osteodystrophia fibrosa.

The recent work of Hunter (19) in this country, and of Snapper (62) and others in Austria, has shown that generalized fibrocystic disease is a separate affection with distinct biochemical and radiological findings ; with a definite aetiological relationship to tumour of the parathyroid gland ; and amenable to surgical treatment.

No changes of the parathyroid are associated with osteitis deformans and the removal of the glands in two cases (62) had no effect on the disease.

Biochemical Investigations

Historical. Until quite recently, biochemical methods have been but infrequently used in the study of osteitis deformans. Da Costa (9) thoroughly investigated two cases in Philadelphia and found a definite retention of Ca, Mg, and P_2O_5 in both cases with a marked loss of S in one case only. Kay (18) (*Journ. Chem.* 1930, lxxxix. 249) examined twenty-one cases for the phosphatase content of the blood plasma and found values between 0.65 and 3.2 (normal average 0.15). The phosphatase value was found to be roughly correlated with the severity of the disease as estimated clinically and from the radiograms. It was noted that the phosphatase was high, even after twenty-five years' duration, and that there was comparatively little excretion of the enzyme in the urine: the amount in the cases examined being 1-4 times that in normal urines. Kay found no abnormality in the amount of the 'ester' phosphorus fraction of the blood, i.e. the substrate for phosphatase.

Barrenscheen and Gould (63) determined the Ca content of the serum and urine in four cases of Paget's disease and found the former to be 13.8, 13.8, 11.5, and 11.2 mg. per cent., and the daily urinary Ca to be 0.264, 0.302, 0.155, and 0.426 grm. as compared with 0.180-0.250 grm. in a series of normals. The serum Ca was determined by a process not in general use in this country and the results are not strictly comparable with those recorded later in this paper. Hunter (19) reported the serum Ca, plasma P, and phosphatase in seven cases. The Ca was 8.4-10.8 mg. per cent.; P, 3.0-3.5 mg. per cent.; and the phosphatase 0.66-1.4 units per c.c.

Five cases, four old and one florid, have recently been investigated by Lasch (17). Bence Jones protein was absent in the urine and the usual tests for syphilis were negative. The gastro-intestinal canal, liver, and kidneys were normal. After an injection of 10 per cent. calcium chloride solution the return of the serum Ca to normal was markedly delayed; in three cases there was a slight increase in the serum Ca, low urea values, and increase of cholesterol. Otherwise the biochemical results were within the normal range.

The basal metabolic rate was found by Boothby and Sandiford (64) to be within +15 per cent. and -15 per cent. in five out of six cases.

Methods of Analysis. Blood. Calcium was determined by the Tisdall modification of the Kramer-Tisdall method (65) and inorganic phosphorus by the Benedict modification of the Bloor process (Myers, 66).

Phosphatase was estimated by the original Kay process (67) with slight modifications introduced by one of the authors (Race, 68). In accordance with the recommendations of Kay, oxalated plasma was used, but a comparative test with serum was also made on a number of samples. All the results given in this paper were obtained with oxalated plasma, but in view of the fact that, in a series of twenty-six samples, serum gave a higher

phosphatase figure in every sample, it seems desirable that in all future work of this description serum should be employed. The average serum phosphatase was 17 per cent. higher than that of the oxalated plasma, a figure much greater than can be ascribed to shrinkage due to the oxalate.

TABLE VIII

Blood serum.				Urine.			Plasma phosphatase.
Name.	Ca.	P.	Ca × P.	Ca. mg. per diem.	$\frac{\text{T.N.}}{\text{P}_2\text{O}_5}$	$\frac{\text{P}_2\text{O}_5}{\text{Ca.}}$	
Group I							
C. H. B.	10.2	3.41	34.8	0.294	5.4	6.8	0.27
J. Me.	10.1	3.3	33.4	0.334	5.5	3.9	0.56
				0.445	8.1	1.9	0.76
							0.51
T. H.	10.4	2.45	25.6	0.296	5.5	4.9	1.35
				0.360	4.6	5.6	1.46
G. A. G.	9.7	3.56	34.6	0.381	5.1	3.9	
	10.2	3.84	39.2	0.426	6.1	4.9	1.22
				0.356	6.1	3.9	1.24
J. W. B.	10.4	3.40	34.6	0.538	5.3	3.2	0.46
				0.314	6.9	4.7	0.64
P. H.	10.3	3.5	36.2	0.322	5.2	6.4	0.52
J. A. W.	10.1	3.65	36.8	0.358	5.3	4.0	0.70
S. W.	10.1	3.2	32.3	0.270	5.2	4.8	0.25
J. McK.	9.8	3.3	32.4	0.314	4.4	6.5	0.24
Group II							
T. G.	10.6			0.240			2.15
J. T.	10.1	2.0	20.2	0.197	5.6	10.2	0.58
J. Mn.	11.3	3.08	34.8	0.200	5.75	9.4	0.35
				0.220	6.1	8.1	0.23
							0.24
J. Mgn.	9.9	3.95	39.3	0.192	6.05	8.4	1.97
S. J. B.	9.6	3.6	34.5	0.195	6.35	6.2	1.79
S. G.	10.3	3.68	38.2	0.184	5.7	6.8	1.00
T. Hn.	9.9	2.84	28.2	0.231	5.8	6.25	0.34
W. W.	9.5	3.33	31.7	0.220	6.3	7.5	0.21
Group III							
C. H.	9.8			0.117	4.9	11.8	1.34
							1.26
O. T.	9.8	3.88	30.4	0.097	6.8	11.9	1.32
	10.2	3.18	32.5	0.098	7.3	15.5	2.96
	10.2	3.5	35.7				3.14
							3.77
E. B.	9.7	3.72	36.0	0.147	8.2	7.7	3.14
							4.30
T. C.	9.8	3.42	33.6	0.070	6.6	21.8	1.87
				0.130	5.5	13.2	2.23
				0.145	6.4	11.7	

Further experiments indicated that the minimal amounts of pot. oxalate required to prevent clotting had a measurable retarding effect on the velocity of the enzyme reaction and that it could be neutralized by the addition of an equivalent amount of CaCl₂. In some experiments a further addition of CaCl₂ gave a higher phosphatase value, but the increase was very

small and variable. The optimum concentration of CaCl_2 calculated as Ca was 0.005 M., which is somewhat higher than that reported by Kay (69).

The Suspension Stability was estimated by the technique of Cooper (7) using 15 c.c. graduated centrifuge tubes and pot. oxalate as the anti-coagulant.

Urine. For the determination of Ca, the method of Shohl and Pedley (71) was found to give results that did not check well in some cases with the nitric acid incineration process and was abandoned in favour of the following modification of the method of Inoue (72).

2-4 c.c. of the sample, the amount varying with the concentration, were placed in a 15 c.c. centrifuge tube and five drops of 20 per cent. ammonium acetate solution with a pH of 5.7, and 1 c.c. of saturated ammonium oxalate added; after adding sufficient water to bring the total volume to about 5 c.c., the contents of the tube were mixed and allowed to stand overnight. The precipitated calcium oxalate was washed and titrated with 0.01 normal solution of KMnO_4 as in the Tisdall process for blood serum.

The error with this method as compared with the HNO_3 incineration process before precipitation of the Ca as oxalate was found to be ± 20 per cent.

Results. The Ca content of the serum varied from 9.1-11.3 mg. per cent. (*vide* Table VIII), but in the great majority the results were between 9.5 and 10.5 mg. per cent. The figures show no variation from the normals investigated in this hospital (88) and accord with those found by Hunter (19). No evidence of the slight hypercalcaemia reported by Koechig (73), Barrenscheen and Gould (63), and Lasch (17), has been discovered, and it is possible that the slightly increased values found by the latter workers are to be attributed to the method used for analysis. The de Waard process used by them gives, in the hands of various continental workers, about 1 mg. of Ca per 100 c.c. higher than those usually obtained in this country with the Tisdall process. According to Kylin (74) the range in healthy persons with this process is 10.5-12.0, but others place the upper limit at 13 mg. per cent.

The serum inorganic phosphorus showed somewhat greater variations (2.0-3.95) than were found by Hunter, but in the majority it was within the normal limits, and the abnormal results could not be correlated with any other finding.

In all the cases the product $\text{Ca} \times \text{P}$ has been calculated in order to ascertain if there is any correlation between the potential bone-forming elements in the blood and the radiographic and biochemical findings. In children the $\text{Ca} \times \text{P}$ product is usually not less than 40 and lower values are generally regarded as indicative of rickets, but when the growth of bone has ceased the product falls to 30-35.

The $\text{Ca} \times \text{P}$ product in this series of cases is usually within the normal limits, and the abnormal results bear no relation either to the amount of circulating phosphatase or to the urinary excretion of Ca.

Holt, La Mer, and Chown (75) have suggested that, inasmuch as bone is largely $\text{Ca}_3(\text{PO}_4)_2$, the ionic product $[\text{Ca}^{++}]^3 \times [\text{PO}_4^{---}]^2$ should be a better

criterion of the potential bone-forming ability than the usual $\text{Ca} \times \text{P}$ product. Although this has some advantages, it must be remembered that only a portion of the Ca is ionized and that, at the normal pH of blood, only a small fraction of the P is in the form indicated in the formula for the ionic product, i.e. $[\text{PO}_4^{'''}]$.

It has also been shown both theoretically and experimentally by Shear and Kramer (76) that the pH is an important factor in calcification.

Kramer et al. (77) found that calcification *in vitro* could not be obtained with a $\text{Ca} \times \text{P}$ of 50 when the pH was below 7.0.

The ionic product in the form $[\text{Ca}]^3 \times [\text{P}]^2$ has been calculated in this series, but as it throws no additional light on the problem the results have been omitted from the table.

Urine. In Table IX, in addition to the total nitrogen (T.N.), inorganic phosphate (P_2O_5), and calcium (Ca) found in the urine in twenty-four hours, the T.N./ P_2O_5 , and $\text{P}_2\text{O}_5/\text{Ca}$ ratios are also given because the absolute values will vary in some degree with the amount of foodstuff ingested. All the patients received the same diet, but the total amount would vary somewhat with the body-weight and other factors.

The ratios are summarized in Table IX with similar results obtained with healthy normals (A), and with hospital cases showing no evidence of bone dystrophies (B), which are added for comparison.

TABLE IX

	Ratio T.N./ P_2O_5 .		Ratio $\text{P}_2\text{O}_5/\text{Ca}$.		Ratio Ca mg. diem.	
	Average.	Range.	Average.	Range.	Average.	Range.
A. Healthy normals	5.2	4.5-6.5	10.4	8.8-12.0	0.234	0.201-0.262
B. Hospital cases	6.8	4.5-9.1	8.0	6.2-10.7	0.171	0.148-0.197
C. Osteitis def. I	5.6	4.4-8.1	4.6	1.9-6.4	0.358	0.270-0.538
" " II	5.9	5.6-6.3	7.8	6.2-10.2	0.209	0.184-0.240
" " III	6.6	4.9-8.2	13.4	7.7-21.8	0.115	0.070-0.147

From the above results it will be seen that although the T.N./ P_2O_5 ratio in Paget's disease shows greater variations, particularly in Group I, than was found in healthy normals, they are not greater than in the hospital cases showing no evidence of bone dystrophy, and that the mean value of the ratio is approximately constant in all three groups and shows no marked deviation from the normal. Da Costa (9) obtained similar ratios in the two cases examined, viz.: 6.4 and 5.75.

The calcium results show three well-defined groups having high, normal, and low urinary calcium excretion respectively, and confirm the apparently conflicting results of Da Costa (9) who found the daily average Ca in the urine in two cases to be 0.016 and 0.065 gr. and those of Barrenscheen and Gould (63) who found one low and three high values.

It should be mentioned that Da Costa et al. did not regard a Ca retention as characteristic of the disease, for they stated:

'At the same time we have no basis for saying that the bones in osteitis deformans will always, under all conditions exhibit an increased content of calcium. . . . We must also bear in mind the possibility that at different stages of osteitis deformans the individual will react differently metabolically and that the bones will vary in composition according to the status of the disease. . . . At one stage we may have an osteoid formation which possesses a low Ca content, and as the disease progresses this pliable osteoid matrix, principally organic in character, may change materially in composition through subsequent calcification. During the formation of the uncalcified osteoid matrix such an individual would probably show no pronounced tendency to retain Ca, whereas when calcification was at its height a very marked retention might be demonstrable.'

An acid-producing diet may produce decalcification of the skeleton, but the pH values of the twenty-four hour urine samples eliminates this as a possible factor in our cases. The average values are:

	pH
Group I	5.8
„ II	5.9
„ III	5.4

Renal function. As determined by the specific gravity fixation test there was no impairment of renal function in any of the sixteen patients examined.

Phosphatase. The phosphatase figures are also given in Table VIII, from which it will be seen that there is an increase in every case compared with the values of 0.11–0.19 obtained with healthy normals.

As all our cases were sent to this Hospital with a diagnosis of 'rheumatism', and a number of them were suffering from some form of 'rheumatic' complication (vide Table III) in addition to osteitis deformans, the plasma phosphatase content of the plasma was estimated in various rheumatic and allied conditions and has been reported by one of us (Race, 68). The results show that in none of the cases of osteitis deformans could the increased phosphatase be ascribed to the concurrent condition. The only disease in the rheumatic group with an abnormal phosphatase is spondylitis ankylopoietica in which ossification of the ligaments is a characteristic feature.

Taken as a whole there is a rough correlation between the phosphatase content of the plasma and the intensity of the symptoms and radiographic findings, a relation first noted by Kay (18) and extremely suggestive that the enzyme is associated with calcification.

Since Robison (78) first demonstrated in 1923 that growing bone contained an active phosphatase, a very considerable amount of experimental work has been carried out on this subject. The evidence as to the relation of the enzyme to ossification of bone has recently been summarized by Kay (18) and appears decisively in favour of the view that the two are intimately related. Whilst we agree with Kay that the increased phosphatase

is secondary to the disease and not a cause of it, we cannot concur with the suggestion that 'the continual leakage of enzyme from the bone in osteitis deformans may be the cause of the irregular deposition of new bone outside the normal limits (e.g. in the skull) which is so characteristic of the disease'.

Discussion

As mentioned above, the cases can be divided into three groups according to the urinary output of calcium, but we consider that the disturbance of the calcium metabolism is only a secondary manifestation of this disease. It seems probable that the disease is one of the reticular tissue of the bone and that, due to the morbid process occurring in this tissue, the calcium salts are removed from the affected area and that later, when this process has passed off, recalcification occurs and new bone is formed as a reparative process. Two processes will, usually, be proceeding simultaneously: the first a removal of calcium salts at one or more sites followed by the second phase in which recalcification takes place in the wake of the former one. The calcium balance will depend upon which of these phases predominates when all affected areas are considered. In cases with a high urinary calcium the decalcifying process is in the ascendancy, not necessarily in any localized area, but in the diseased areas as a whole. In the cases with a low urinary calcium output the calcifying process predominates, and in a large group of cases these processes are in equilibrium and the urinary calcium output is normal although the disease may be still active.

With the exception of two cases in Group I in which the high calcium excretion is associated with little or no calcification as judged by the radiograms, there is no general correlation between the calcium excretion in the urine and the radiographic appearances in Groups I and II. In Group III the low urinary calcium is associated with very definite increased calcification of the bones, but the converse, that increased opacity to X-rays is associated with a low urinary calcium, does not obtain. The relation of the calcium figures to the radiographic appearances can best be appreciated by bearing in mind that whilst the former represents the balance of the processes occurring at the moment of examination, the latter represents the summation of the processes that have occurred in the bones since the commencement of the disease. The relation of the two will obviously be very variable, but one would anticipate that in the early stages of the disease some cases would give an increased calcium output with little or no radiographic changes, and that in the advanced cases marked opacity to X-rays would be found associated with low urinary calcium.

From the facts that extreme porosis of the bones over a large area is rarely found in the radiograms, and that spontaneous fractures occur in a minority of cases, we must conclude that the phase of excessive output of calcium in the urine must be more or less transient. If the weight of the

dry skeleton is taken as 5 kilos and the Ca content as 20 per cent. the total Ca is 1 kilo. A loss of 100 mg. per diem would represent 36.5 grm. per annum, or 3.6 per cent. of the total calcium of the skeleton, a comparatively low figure compared with the 20 per cent. which a cow may lose during the lactation period (Cameron, 79). Although three cases have been under observation for fourteen, sixteen, and seventeen months respectively we have no evidence that any one of them has changed from a high urinary Ca to a low one, or vice versa, but other evidence indicates that the former change must occur. This evidence is (1) the general tendency during the course of the disease is that the radiograms show increased density and size of the bones, and (2) the bones increase in weight and also in the proportion of calcium.²

Whilst it is conceivable that the increased opacity to X-rays may be due to alterations in the composition of the new bone laid down, such an explanation is highly improbable. Bone is generally regarded as a mixture or compound of $\text{Ca}_3(\text{PO}_4)_2$ with a small proportion of CaCO_3 and if the ratio of these is altered it is conceivable that the new mixture may have a reduced penetrability to X-rays. The determination of the total Ca in the bone ash would not assist in the solution of this problem as the total substitution of CaCO_3 for $\text{Ca}_3(\text{PO}_4)_2$ would only increase the total Ca by one per cent.

Decalcification produced by chloride acidosis was found by Goto (80) to result in a loss of CaCO_3 but not of $\text{Ca}_3(\text{PO}_4)_2$ in rabbits.

No recent determinations of the ratio of Ca/P in Pagetized bones have been made, but seven out of eight specimens of pathologically calcified tissues examined by Kramer and Shear (81) showed no variation from that found in normal bone and no material variation in the proportion of CaCO_3 . By analogy there is no reason to assume that the secondary calcification in Paget's disease differs in chemical composition from the primary one which it has replaced.

Normal human bones, according to McCrudden (82) and Robin (83), contain 20-21 per cent. of Ca calculated on the dry matter, and although some workers (Higbee and Ellis (8)) have maintained that the increased development is not accompanied by calcification no analytical evidence is adduced in support. On the other hand, several French observers have found that the proportion of inorganic matter in the bones is definitely increased (Tourette and Magdelaine (84), Munier (85), and Robin (83)). Tourette and Magdelaine found 30.1 per cent. of Ca in a Pagetized clavicle and also a second metacarpal bone with a weight 700 per cent. greater than the normal.

The balance of the evidence is strongly in favour of the view that the increased opacity to X-rays is due to the presence of a larger amount of

² Since this paper was submitted for publication we have obtained evidence of this change in one case. S. H. Male, in Nov. 1930, showed a phosphatase value of 2.05 with a urinary output of Ca 6.238 gr. In April 1932 the phosphatase had increased to 3.15 and the urinary Ca had fallen to 0.067 gr.

bone and a greater Ca content, the chemical composition of the inorganic portion of the bone being unaltered.

With the exception of Group III, in which very high phosphatase figures are associated with a low Ca in the urine, the phosphatase content of the plasma is very variable, some high and low figures being found in both of the other groups.

The extensive experimental work of recent years on ossification has shown very clearly its association with the enzyme phosphatase, but there is no evidence that ossification can be initiated by this enzyme and it is probably a product of cell metabolism which diffuses out and is carried away in the general circulation.

The excess of phosphatase found in the blood indicates an active process, and although there is a general correlation between the intensity and extensity of the bony changes as judged from the radiograms, and the excess of phosphatase, there are some notable exceptions to this generality. In each of Groups I and II there are two cases in which the phosphatase is almost normal and in which the radiographic changes are indubitable. We consider such cases in Group I as ones in which, at present, active decalcification is occurring with but little attempt at recalcification. The morbid process has probably been quiescent and a fresh cycle of activity has commenced. The low phosphatase in two cases in Group II, also associated with characteristic bony changes, suggests that they are almost in a quiescent stage.

Blood. Haematology. In none of the cases examined was there any evidence of a change either in the number of R.B.C.s and W.B.C.s, or in the haemoglobin content; a result also noted by Lasch (17). Apart from a marked eosinophilia combined with lymphocytosis in one case, this worker found no marked deviation from the normal in the blood picture, but it will be seen from Table X that in the majority of our cases we observed a distinct monocytosis, a result also indicated by the differential counts given by Da Costa (9).

The weighted mean (W.M.) of the Cooke-Arneth count shows a shift to the left in all the cases. Whilst the excess of immature types of polymorphs can be attributed in some cases to concurrent disease, the fact that it persists in seven cases in the absence of any detectable sepsis strongly suggests a disturbance of the bone-marrow. The monocytosis may also be a secondary phenomenon originating in a similar manner.

Suspension stability (S.S.). The exact nature of the changes that cause R.B.C.s to form rouleaux and so sink more rapidly are unknown, but it is well established that the stability of the suspension of the red cells in healthy persons is high and that it is lowered by extensive reactions to infections and toxins. In the rheumatic group of diseases, for example, the S.S. is low in infective arthritis and subacute rheumatism; slightly low in fibrositis; and normal in such myopathies and neuropathies as lumbago and sciatica (Race (86)).

In our cases of osteitis deformans the S.S. is low in the cases with concurrent disease and sepsis, but in the others the usual relation between the S.S. and the W.M. of the Cooke-Arneth count found in rheumatic diseases by Hill (87) is absent. Lasch (17) found an increased 'Senkungsreaction' (decreased S.S.) in all the five cases examined by him, but the figures obtained with our cases show that this is not a constant feature of Paget's disease. We would emphasize the fact that in the seven cases free from concurrent disease and in which no demonstrable septic focus could be found, the S.S. was quite normal: a finding that is strong presumptive evidence that osteitis deformans is not one of the 'infective group' of diseases.

TABLE X

Blood Examination

Case.	Large lymphocytes.	Small lymphocytes.	Monocytes.	Cooke-Arneth W. M.	S.S.	Concurrent disease and/or sepsis.
Group I						
J. Me.	5.8	31.7	12.7	1.98	64	Present
T. H.	12.5	20.5	10.2	1.90	91	Absent
G. A. G.	4.8	21.1	13.8	1.96	98	"
J. W. B.	11.8	26.8	10.5	2.07	65	Present
P. H.	11	25	10	2.3	87	Absent
S. W.	5	13.7	7.9	1.83	62	Present
J. H. W.	8	21.7	10.8	2.11	92	Absent
J. H. McK.	7.5	18	7	2.4	51	Present
Group II						
T. G.				2.04	77	Present
J. T.	3	10	14	2.11	90	Absent
J. Mn.	11.0	12.3	11.7	1.89	85	"
J. Mgn.	12.3	9.6	9.6	2.25	75	Present
S. J. B.	18.4	28.1	10.1	1.77	54	"
S. G.	8.6	34.4	7.7	2.09	73	"
T. Hn.	6.8	23.4	8.0	2.27	78	"
W. W.	6.7	20.6	14.0	1.81	69	"
Group III						
C. H.	16.0	27.5	1.5	1.80	86	Absent
O. T.	2.5	30.5	4.9	2.01	51	Present
E. B.	9.3	22.2	7.8	1.85	58	"
T. C.	11.5	29.2	11.7	1.94	73	"

Chemical. The calcium content of the serum was within the normal limits in all cases and the inorganic phosphorus was also normal, with the exception of two cases in which there was a slight deficiency. These results are in marked contrast with the high calcium and low phosphorus found in osteitis fibrosa (generalized) and greatly assist in the differential diagnosis of the two diseases.

In addition to the biochemical results recorded above, we have made others with entirely negative results: there was no evidence of urea retention or significant changes in the carbon dioxide content or pH of the plasma; the plasma total protein was normal and any changes in the

albumin/globulin ratio were those associated with concurrent disease and/or sepsis.

If our investigations are considered in conjunction with those of other workers we think that we are justified in concluding that such abnormal manifestations as have been discovered may be attributed to the partial disturbance of metabolism of a healthy organism by a localized disease process in the bones.

We regard the disease as a local one primarily affecting the reticular cells of the bones. It has a close relationship to the reticulo-endothelioses and the analogy of Hodgkin's disease is suggestive.

Treatment

Paget treated his patients with potassium iodide and liquor potassae, but was not enthusiastic over the results. These drugs, with the addition of 'the bark' and mercury, continued to be used as the treatment for this disease. Occasionally a temporary improvement in the symptoms was claimed, but we are of the opinion that this was due to the rest in bed which formed part of the treatment, rather than to the drugs administered. No case showing permanent improvement is recorded.

Nicory (89) in 1930 announced excellent results from general ultra-violet radiation. There were no biochemical controls on his cases, but improvement was claimed in the radiograms. Our experience with this treatment does not confirm this finding.

Working on the hypothesis outlined in the preceding section we decided to try the influence of arsenic on this disease.

The general condition of several patients rendered them unsuitable for such treatment, and up to the present we have only been able to study the effect of arsenic in four cases. The results are given in Table XI.

TABLE XI

Patient.	Duration of treatment.	Phosphatase.		Urinary calcium.	
		Before treatment.	After treatment.	Before treatment.	After treatment.
W. B.	21 days	0.92	0.64	0.545	0.314
T. H.	60 "	1.35	0.82	0.296	0.279 ^a
J. W.	30 "	0.29	0.12	—	—
T. C.	60 "	2.23	1.87	0.130	0.070

One patient (T.H.) has been under observation for six months and shows a definite clinical improvement.

The cases are too few and remained under observation for too short a period to form a definite opinion on the merits of this treatment, but we think that it is promising and deserves a prolonged trial in a larger number of cases.

^a After further treatment the urinary Ca has fallen to 0.191 gr. per diem.

Summary

1. Osteitis deformans is a separate disease with no relationship to osteitis fibrosa (generalized).
2. The incidence is greater than is commonly supposed.
3. The course and duration vary widely and it may be present for considerable periods without signs or symptoms.
4. There are no constant complications, but the association with osteosarcoma is high.
5. The radiographic changes are characteristic.
6. The blood phosphatase is increased and the serum calcium and phosphorus are always normal.
7. The urinary calcium may be high, low, or normal.
8. The suspension stability of the blood is normal except when there is concurrent disease or sepsis.
9. Haematologically, there is often a monocytosis but no change in the number of R.B.C.s and W.B.C.s; the haemoglobin is normal.
10. A treatment is described which has modified the biochemical findings.

In conclusion we would acknowledge our indebtedness to the Honorary Medical Staff of the Devonshire Hospital for placing their cases at our disposal, and particularly to Dr. C. W. Buckley for access to private cases and his encouragement throughout the course of this investigation. We also desire to express our appreciation of the excellent radiograms furnished by Mr. Gibson, the Radiographer, and for his assistance throughout this work.

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FIG. 1. Tibia (T.C.). Showing an increase in thickness and bowing of the bone. The outline is hazy. There is coarsening of texture with accentuation of the bone lines in the longitudinal direction, an irregular increase in density, and some clear areas



FIG. 2. Tibia (O.T.). The outlines of the bones are hazy. There is a loss of normal bone texture, which has become coarsened with accentuation of the longitudinal fibres, and an irregular increase in density



FIG. 3. Skull (J.K.). The bones of the vault show some haziness and loss of outline, and are thickened. The normal bone texture has been replaced by a 'cotton-wool' appearance. Several circular areas of bone will be noticed surrounded by sharply defined clear circles in which marked decalcification has occurred, and which have been described in the text under the term 'osteoporosis circumscripta'.



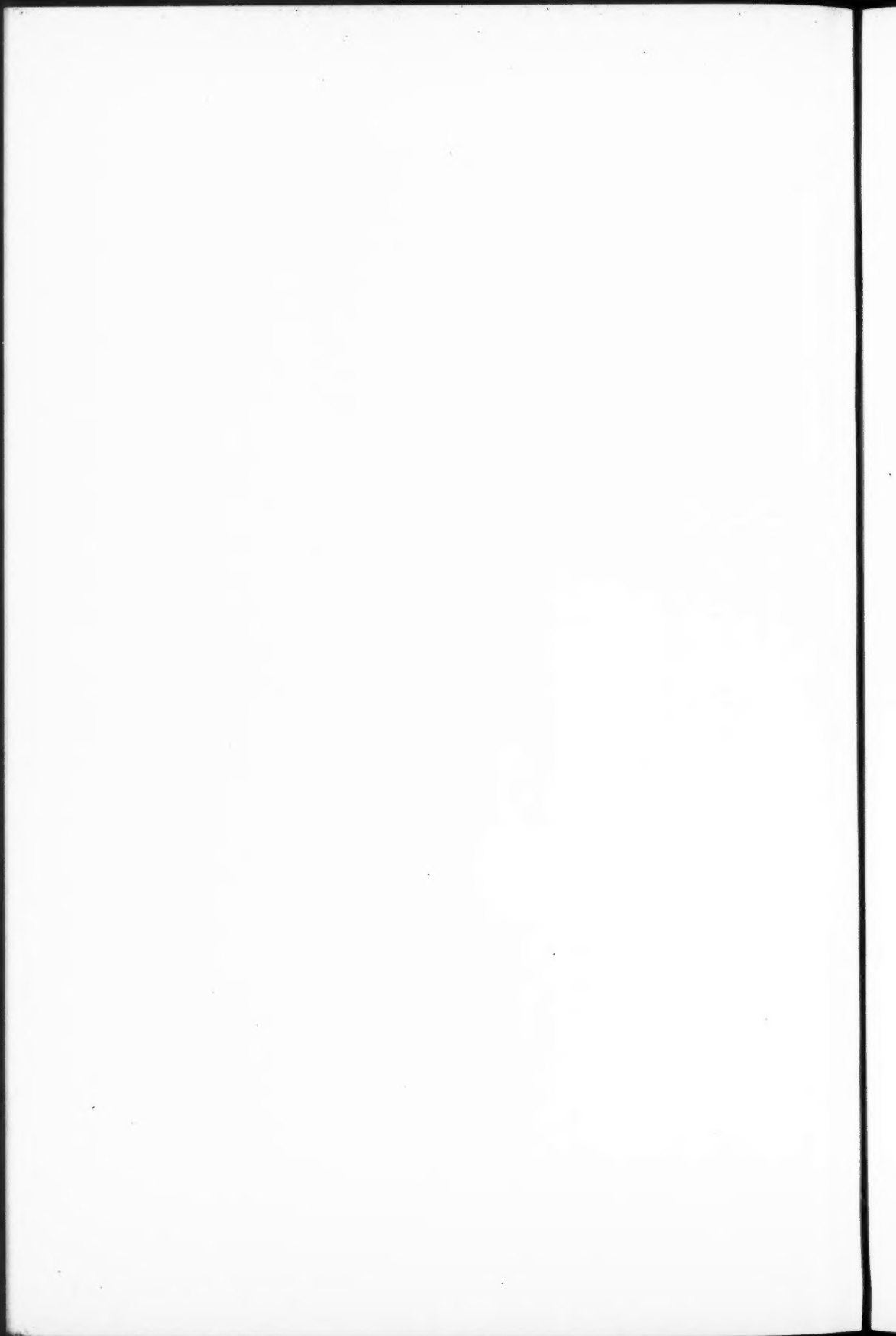
FIG. 4. (W.B.). Illustrating the disease in the early stage. The bones are undergoing decalcification which gives them a coarsened appearance. Streaming of the bone lines will be noticed along the iliac crest and in the sacrum. A cloud-like appearance is developing along the right pelvic brim

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FIG. 5. (A.S.) The right side of the pelvis only is affected and contrasts with the normal appearance of the left side. The ilium has a coarsened appearance with accentuation of the bone lines. It is undergoing decalcification and loss of normal texture. Clouding is commencing along the right pelvic brim



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THE EFFECT OF REMOVAL OF SEPTIC FOCI ON THE COURSE OF NEPHRITIS¹

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WITH the exception of a few cases caused by mercury, cantharides, and other poisons, nephritis is a disease which stands in close relationship with infections of various kinds, and appears to be caused by the action of bacteria or their toxins. In the majority of cases of acute nephritis, including the scarlatinal ones, the disease follows an acute streptococcal tonsillitis, and occurs most usually from one to three weeks after the throat infection.

On the other hand, acute nephritis may occur in the course of a more or less chronic infective condition of the nasopharynx, skin, or elsewhere, as in children with chronic tonsillitis, suppurative otitis media, or eczema and impetigo, without any acute exacerbation of the infection having been observed.

In adults a greater variety of septic foci is commonly found in relation to nephritis, as for instance, alveolar abscess, maxillary sinusitis, and pelvic infections in women. A certain number of cases of bacterial infection of the urinary tract also develop a true glomerular nephritis which in my experience is often very resistant to treatment.

In the aetiology of the more chronic and insidious forms of renal disease, classified as subacute or chronic glomerulo-nephritis, nephrosis, and malignant nephrosclerosis, there is also little doubt that sepsis plays an important part, and many authors have commented on the frequency with which pneumococcal infections are found in relation to nephrosis, since this was first pointed out by Fahr (1). Nevertheless there are some cases of nephritis in which it is not possible to trace a septic focus of any kind either during life or at post-mortem examination.

Occasionally the removal of a septic focus—such as the operation of tonsillectomy—is followed by the development of acute nephritis, in this case presumably on account of temporarily increased absorption of toxins consequent upon the operation.

The recognition of this relationship between nephritis and infections has led to the removal of septic foci becoming part of the treatment of the disease, and most text-books and monographs dealing with the treatment of

¹ Received June 20, 1932.

acute nephritis now recommend that septic foci should be sought for and, if possible, dealt with during the period of convalescence, or the stage of remission from acute symptoms.

In 1929 a short series of cases illustrating the results of such treatment was published by the author (2), but the most exhaustive study of the subject so far is that of Kollert (3), who deals fully with the relation of sepsis to nephritis, the diagnosis of septic foci, and the results of operations for the treatment of sepsis. Whereas many of his records show clearly the immediately beneficial results of such treatment, they are not compared with records of cases treated otherwise, and they include cases of both acute and chronic nephritis, so that it is difficult to assess the value of his results. Other authors such as Boyd (4) and Guild (5) mention the removal of sepsis as favourably influencing the prognosis in acute nephritis, but do not attempt to estimate the results of this procedure separately.

Lyttle and Rosenberg (6) stress the importance of the persistence of sepsis as a cause of chronicity in nephritis, but state that 'careful attention to diet . . . and a vigorous effort to remove or treat foci of infection did not have any effect in preventing further acute exacerbations'. They give no case histories or statistics to support this view, however.

Römcke (7) has recently recorded some cases of chronic nephritis in which marked improvement occurred after septic foci were removed.

With a view to obtaining further information on the subject I have followed up a series of cases of nephritis admitted to the Royal Infirmary, Sheffield, during the years 1924-29 inclusive. Owing to the difficulties of classification I have included every case of nephritis admitted within a few days or weeks of the onset of the disease and in whom no signs of chronic nephritis could be demonstrated on admission. The series thus includes cases that were variously diagnosed as acute haemorrhagic nephritis, acute glomerulo-nephritis, subacute glomerulo-nephritis, and nephrosis. Although under the care of the several physicians to the Royal Infirmary (and I am indebted to my colleagues for the use of their records and permission to publish their cases) the treatment of the patients was similar with regard to diet, nursing, and drugs.

I have personally examined all these cases during their stay in hospital, and most of them again in 1928. During March and April 1932 I have again examined all the patients who can still be traced.

In Table I these cases are arranged in several groups according to whether or not they were treated by removal of septic foci. Thus in the cases of the first group a septic focus was definitely shown to be present, but was not eradicated. In the second, though many of the cases were connected with an infective illness at the commencement, no surviving focus of sepsis was discovered on re-examination. In the third group are cases where a septic focus was found to be present and was successfully removed. In the majority of instances this consisted of the removal of septic tonsils, or tonsils and adenoids, usually carried out during the stage of remission after the

acute symptoms had subsided. In some cases, however, septic foci were removed at a later date in the illness, either owing to a recurrence of the nephritis or because of the unsatisfactory course of the disease. There remains the small group in which nephritis followed the eradication of sepsis, namely tonsillectomy in two cases, and mastoid antrotomy in one. This last case (No. 252) is the only one of the series in which the removal of sepsis can be considered to have had an unfavourable effect, though a temporary return of haematuria after operation is often noticed.

TABLE I

	No. of cases followed.	Well.	Doubtful.	Ill.	Recurred.	Died.	Not traced.
Group 1							
Septic focus not re- moved	36	16	2	5	7	6	23
Group 2							
Septic focus not found	33	16	2	2	6	7	
Group 3							
Septic focus found and removed	23	22	0	0	0	1	3
Group 4							
Nephritis followed re- moval of septic focus	3	2	0	1	0	0	0
Total	95	56	4	8	13	14	26

The results are interesting in demonstrating the fate of nearly 100 new cases of nephritis. Included in the column headed 'well' are the patients who are now free from any symptoms referable to kidney disease and have a normal blood-pressure, retina, heart, and urine, the last-mentioned having been examined chemically and, in all cases of uncertainty, microscopically. Under 'doubtful' are patients who, though free from signs of kidney disease, state that they suffer from swollen eyelids occasionally or from some other suggestive symptom. A few patients in this column are cases of urinary tract infection without signs of nephritis at present, and one or two cases where the blood-pressure was found to be above normal, despite the absence of other signs or symptoms.

Under the heading 'ill' are chiefly cases of progressive chronic nephritis with pallor, albuminuria, high blood-pressure, and usually retinitis and signs of renal failure.

With regard to the recurrences, most of these patients are well at the present time. They are classified in Group 3 as 'well' if the nephritis has not recurred since the removal of their septic foci.

The results appear to indicate the favourable course of the cases in which septic foci have been dealt with, but, as they are based on a mixed series of cases, are obviously not to be relied upon in their crude form.

For instance, some of the deaths occurred during the acute stages of the disease, before removal of septic foci could have reasonably been carried out.

These tend to vitiate the results of the first group. Then there are included a number of cases of that most serious form of nephritis which usually starts too insidiously to be called acute, and runs a progressive and relentless course. Cases of nephrosis, too, are obviously not comparable with the acute cases, and in all these severe forms there has been less tendency in this series to remove septic foci, as the condition of the patient has seemed too serious to warrant operative interference. From experience of later cases I am doubtful whether this hesitation to remove sepsis is wise, but for the present purpose the results in this subacute type of case cannot be considered along with the others.

TABLE II
Acute Nephritis

		Total no. of cases followed.	Well.	Doubtful.	Ill.	Recurred.	Died.
Group 1							
Septic focus not removed	No. of cases	30	16	2	4	7	1
	Average age	13.5	10.5	18	15.7	19	5
	Average days in hospital	37.5	36.5	36.5	36	40	42
Group 2							
Septic focus not found	No. of cases	28	16	2	2	6	2
	Average age	17.2	18.3	18.5	14.5	13.3	21.5
	Average days in hospital	38.6	39	45.5	48.5	31.7	41
Group 3							
Septic focus found and removed	No. of cases	22	22	0	0	0	0
	Average age	14.3	14.3	0	0	0	0
	Average days in hospital	38	38	0	0	0	0
Group 4							
Nephritis followed re- moval of septic focus	No. of cases	3	2	0	1	0	0
	Average age	8.3	8	0	9	0	0
	Average days in hospital	42	32	0	62	0	0

In order to obtain the results of treatment of cases as far as possible strictly comparable one group with another, I have in Table II *excluded* from the series *all cases who never showed a definite remission* (including in that category those who died during the acute stages). By a remission, I mean here the subsidence of the oedema, and marked diminution in albuminuria which is noticeable in most cases of acute nephritis a few days or weeks after the commencement. This remission is usually initiated by a sudden diuresis and a disappearance of any but microscopic amounts of blood from the urine. The remainder of the cases I have classified as before, under the title of acute nephritis.

It is to be noted that only three cases of acute haemorrhagic nephritis (without oedema) are included in the series, two in Group 1 and one in Group 2.

Two very instructive cases (nos. 190 and 225 in the case notes) are not included in either Table because, although a septic focus was removed and the nephritis cleared up, there was a recurrence both of septic infection and of nephritis. They therefore belong to both Groups 1 and 3. No. 190 is of especial interest as the case was one which started as acute nephritis, and developed a pronounced tendency to the 'nephrotic' syndrome with massive oedema, and as much as 20 grms. of protein per litre of urine. Signs of pleural effusion developed which turned out to be due to pneumococcal empyema, and on this being drained under local anaesthesia the whole of the oedema and albuminuria cleared up in less than three weeks. Unfortunately the patient was readmitted three weeks after discharge with pneumococcal meningitis and a return of the oedema and albuminuria, and died in a few days. Nevertheless the case illustrates that, even in apparently desperate cases of the nephrotic type, there may be a complete return to normal if an offending focus of sepsis is found and dealt with. I have again seen this happen in one or two cases too recent to appear in this series.

Consideration of Table II shows as clearly as before that the cases in which septic foci have been removed have run a far more favourable course than the others, since all in Group 3, but only about 50 per cent. of Groups 1 and 2 are well. The criticism may still be raised that the cases of nephritis which start with an acute flare-up of sepsis as a rule run the most favourable course. Whereas this may explain the bad results of Group 2, it cannot explain the discrepancies between Groups 1 and 3 in which the cases would appear to be as strictly comparable as possible. Lest there should be any doubt as to this or as to the selection of cases, the average age and duration of stay in hospital has been stated in the Table, and short notes of all the cases followed up are appended.

The degree of oedema is to some extent an index of the severity of a case of nephritis, and a consideration of the case notes shows that in Group 1 there were seven cases (out of thirty) in which the oedema was of more than average severity (recorded as '+ +'). Only two of these seven have remained well, three have signs of nephritis becoming chronic, and two have recurred. In five out of the twenty-two cases (almost the same proportion) in Group 3, the oedema is recorded as '+ + ' and these are all well.

Finally it should be noted that the cases of so-called subacute nephritis and nephrosis are only excluded from the second Table in order to make the material studied more homogeneous. It is not intended to imply that treatment by eradication of sepsis is not equally applicable to those types of kidney disease.

Summary and Conclusions

A series of cases of nephritis has been followed up with a view to obtaining information as to whether the course of the disease can be influenced by the removal of septic foci.

The results would appear to indicate that the course is favourably influenced by this procedure.

APPENDIX

Notes of Cases

The order followed is :

Sex.

Age on admission to hospital.

Date of admission.

Infective conditions, if any, noted on admission.

Amount of oedema, if any. (+ signifies oedema of slight or moderate amount involving the face and ankles or legs. ++ is a more pronounced oedema, for instance, with slight ascites or oedema of the arms in addition. +++ signifies extreme oedema usually involving the pleural cavities.)

Occurrence of convulsions, if any, in acute stage.

Number of days in hospital (during initial attack).

Condition on discharge. 'Negative' implies no oedema, albuminuria, or haematuria, and does not refer to the presence of septic foci.

Recurrences, if any, and notes on the course of the disease and removal of sepsis if relevant.

Condition on re-examination (and dates of examinations). Here 'negative' implies no septic focus found, as well as no albuminuria, haematuria, oedema, or nephritic symptoms with normal retina and blood-pressure.

The numbers are those in my Case Book and are neither consecutive nor strictly chronological. Missing numbers are cases of chronic nephritis, or cases not traced.

Group 1. Well.

8. F.; 7; Apr. 1927; occasional sore throats; oedema +; I. P. 35 days; negative on discharge; tonsils enlarged, adenitis, 1932. Has rheumatism.

9. M.; 3; Apr. 1927; colds, sore throats; oedema +; I. P. 48 days; negative on discharge; tonsils large, muco-pus in nasopharynx 1932. Has rheumatism.

24. M.; 17; Sept. 1927; oedema +; I. P. 15 days; negative on discharge; tonsils +, muco-pus in nasopharynx, B.-P. 135/88, urine negative 1932.

49. F.; 27; Sept. 1924; tonsillitis, uterine sepsis; oedema +; I. P. 24 days; negative on discharge; sepsis present, otherwise negative 1932.

66. F.; 11; Dec. 1924; oedema +; I. P. 23 days; negative on discharge; tonsils +, otherwise normal 1932.

78. M.; 17; Oct. 1925; tonsillitis; oedema +; I. P. 37 days; negative on discharge; tonsillitis, otherwise negative 1932.

93. M.; 12; Apr. 1925; cold; oedema +; I. P. 41 days; negative on discharge; tonsils +, otherwise negative 1932.

123. M.; 19; Apr. 1926; chill; oedema +; I. P. 43 days; trace albumin on discharge; tonsils + 1928 and 1932, otherwise negative.

138. M.; 2; Sept. 1926; oedema +; I. P. 90 days; negative on discharge; negative except tonsils Oct. 1928.

189. F.; 28; Feb. 1928; 'cold'; oedema +; I. P. 23 days; negative on discharge; negative except tonsils 1931.

214. M.; 7.; July 1928; no oedema; I.P. 26 days; negative on discharge; negative except tonsils and adenoids 1931.

235. M.; 5; Nov. 1928; pus in nasopharynx, middle meatus, and R. antrum treated by nasal washes; oedema ++; I.P. 73 days; negative on discharge; negative except enlarged tonsils 1932.

248. F.; 2; Jan. 1929; otitis media; oedema ++; I.P. 28 days; negative on discharge; negative except ear 1932.

249. M.; 1; Jan. 1929; tonsillitis; oedema +; I.P. 16 days; negative on discharge; negative except tonsils 1932.

250. M.; 8; Dec. 1929; chronic tonsillitis; oedema -; I.P. 28 days; negative on discharge; negative except tonsils 1931.

272. M.; 2; Nov. 1929; otitis media, tonsillitis; oedema +; I.P. 34 days; negative on discharge; negative except tonsils 1932.

Group 1. Doubtful.

58. M.; 14; June 1924; chronic tonsillitis; oedema +; I.P. 21 days; negative on discharge; B.-P. 150/70, urine nil, feet swell occasionally, tonsils septic 1932.

86. M.; 22; Jan. 1925; tonsillitis; oedema +; I.P. 52 days; no oedema, trace albumin on discharge; says occasional swelling of face, no albumin, B.-P. 140, tonsils + 1932.

Group 1. Ill.

72. M.; 7; Feb. 1925; oedema +; I.P. 12 days; no oedema, albumin + on discharge; tonsils septic, albuminuria + 1932.

143. F.; 4; March 1926; oedema ++; I.P. 45 days; trace albumin only on discharge; tonsils +, albuminuria, occasional oedema, 1932.

217. F.; 31; March 1928; oedema ++; I.P. 37 days; negative on discharge; recurred three weeks after discharge, urinary infection found, became chronic. Blood-pressure 220, retinitis, blood non-protein nitrogen 160, blood indican + + +, pericarditis June 1932; all attempts to clear up urinary infection failed.

246. M.; 21; Nov. 1929; L. tonsil enlarged; oedema ++; I.P. 50 days; no oedema, albumin present on discharge; feels well, B.-P. 210, blood non-protein nitrogen 80 mg. indican +, retinitis R. and L, muco-pus L. antrum, 1932.

268. M.; 27; Aug. 1929; tonsillitis and boils; oedema +; I.P. 19 days; trace oedema, albumin 4 grams on discharge; tonsils +; albuminuria + + 1932 (not included in Table II).

Group 1. Recurred.

19. F.; 24; Aug. 1927; quinsy; oedema ++; I.P. 31 days; no oedema, trace albumin on discharge; recurred 1928 (after quinsy); tonsils large, blood-pressure 115, no albumin 1931.

139. F.; 5; July 1926; scarlet fever; oedema ++; I.P. 76 days; negative except tonsils on discharge; recurred two months after discharge and again in 1927; negative except tonsils 1932.

145. F.; 11; April 1926; tonsillitis; oedema +; I.P. 32 days; negative on discharge; readmitted (recurrence) Jan. 1927, oedema, albuminuria

(negative on discharge), tonsils and adenoids +, turbinates +; occasional oedema 1928, 1931, and 1932.

164. M.; 40; Oct. 1926; tonsillitis; oedema +; I. P. 25 days; negative on discharge; recurred 1927 and 1928; tonsils +; pulmonary tuberculosis 1928.

177. M.; 17; March 1927; scarlet fever; oedema +; I. P. 14 days; negative on discharge; recurred 1927 and 1928; large infected tonsils 1928; negative except tonsils 1932.

192. M.; 22; Jan. 1928; tonsillitis; oedema +; I. P. 52 days; negative on discharge; recurrence May 1928; chronic nasal infection, albumin +++ November 1928; negative 1932.

204. F.; 15; June 1928; chronic tonsillitis; oedema +; I. P. 52 days; no oedema, trace albumin on discharge; recurred 1928; Nov. 1928 albumin ++, septic tonsils; not seen 1932.

Group 1. Died.

87. M.; 19; Feb. 1925; tonsillitis; oedema +++; I. P. 42 days; oedema and albumin remained. Died (not included in Table II).

140. M.; 5; Oct. 1926; tonsillitis; oedema +; I. P. 42 days; negative on discharge; recurred Dec. 1926, tonsillitis, oedema +++; died.

162. M.; 58; Aug. 1926; quinsy; oedema +++; I. P. 106 days; oedema and albuminuria continued; died three weeks after discharge. (Not included in Table II.)

231. M.; 16; May 1928; oedema +++, continued for 18 months, the clinical picture being that of 'nephrosis'; nasal polypi were removed, but there was probably also sepsis in the ethmoidal sinuses; later the oedema gradually subsided, polyuria developed and the patient died of uraemia early in 1930 after an operation for acute appendicitis. (Not included in Table II).

265. M.; 19; Nov. 1928; tonsillitis; oedema ++; I. P. 146 days; trace oedema, albumin 9 grams per litre on discharge; readmitted July 1929, 23 days; blood-pressure 230, L. antrum opaque, retinitis. Died uraemia 1930. (Not included in Table II).

271. M.; 17; Nov. 1928; oedema ++; I. P. 220 days; oedema, albuminuria and uraemia on discharge (at request of parents). Septic tonsils, muco-pus in R. antrum (proof puncture). Died a few weeks after discharge. Not included in Table II).

Group 2. Well.

67. F.; 16; Dec. 1924; oedema +; I. P. 39 days; negative on discharge and 1932.

90. M.; 8; May 1925; oedema +; I. P. 26 days; negative on discharge and 1932.

91. M.; 3; Oct. 1925; oedema +; I. P. 18 days; negative on discharge and 1932.

106. M.; 7; May 1925; tonsillitis; oedema ++; I. P. 47 days; negative on discharge and 1928.

141. M.; 1; Sept. 1926; enteritis; oedema +; I. P. 86 days; negative on discharge; negative 1932.

151. M.; 22; Jan. 1926; oedema +; I. P. 17 days; trace albumin only on discharge; negative 1932.

156. M.; 18; May 1926; oedema +; I.P. 28 days; blood and albumin, no oedema on discharge; negative 1928.

180. M.; 14; Jan. 1927; tonsillitis; oedema +; convulsions; I.P. 47 days; negative except trace albumin on discharge; negative Nov. 1928.

186. M.; 15; Feb. 1927; tonsillitis; oedema +; I.P. 105 days; negative on discharge; negative 1928 and 1932.

210. M.; 28; July 1928; tonsillitis; oedema +; I.P. 24 days; negative on discharge and 1932.

213. F.; 24; Apr. 1928; oedema +; I.P. 35 days; negative on discharge and 1932.

240. F.; 42; Oct. 1928; tonsillitis; oedema ++; convulsions; I.P. 68 days; no oedema, albumin present on discharge; negative 1932.

242. M.; 45; Dec. 1928; oedema +; I.P. 36 days; negative on discharge; negative 1931.

260. M.; 19; Jan. 1929; oedema +; I.P. 25 days; negative on discharge; negative 1932.

262. F.; 8; Aug. 1929; oedema +; I.P. 10 days; negative on discharge and 1932.

263. F.; 16; Dec. 1929; oedema +; I.P. 10 days; negative on discharge and 1932.

Group 2. Doubtful.

107. F.; 11; Aug. 1925; oedema +; I.P. 27 days; negative on discharge; occasional swelling of face and legs; not well; urine negative; blood-pressure 140/85, no sepsis 1932.

241. M.; 26; Dec. 1928; oedema +; I.P. 64 days; trace albumin on discharge; negative except blood-pressure 175, 1932 (nervous patient).

Group 2. Ill.

239. F.; 11; Oct. 1928; oedema +; I.P. 59 days; trace albumin only on discharge; recurred 1930; heart enlarged, blood-pressure 130, cloud albumin, no sepsis 1932.

270. M.; 18; Feb. 1929; Pneumonia; oedema —; I.P. 38 days; negative on discharge; no sepsis, albumin 1.5 grams, blood-pressure 140, 1932.

Group 2. Recurred.

21. F.; 27; July 1927; oedema +; I.P. 65 days; no oedema, trace albumin on discharge; recurred (pregnancy) 1928; negative 1932.

39. F.; 6; Apr. 1924; oedema ++; I.P. 44 days; negative on discharge; recurred two months later; negative 1931.

195. M.; 17; Jan. 1928; oedema +; I.P. 21 days; negative on discharge; recurred 1928; negative 1932.

251. M.; 3; Dec. 1929; oedema +; I.P. 26 days; negative on discharge; recurred 1930; negative 1931.

261. M.; 9; Aug. 1929; oedema +; I.P. 17 days; negative on discharge; recurred 1930; negative 1932.

264. M.; 18; Aug. 1929; oedema +; I.P. 17 days; negative on discharge; recurred 1931; negative 1932.

Group 2. Died.

10. M.; 4; Dec. 1926; oedema + + +; I. P. 66 days; negative on discharge; readmitted March 15, 1927; albuminuria and oedema + +; died June 25, 1927; septic foci not looked for.

14. F.; 13; Nov. 1927; oedema + +; I. P. 4 days; convulsions, blood non-protein nitrogen 143 mg. per 100 c.c., died. (Not included in Table II.)

152. F.; 16; Jan. 1926; oedema + + +; I. P. 65 days; oedema and albuminuria continued; died April 1926. (Not included in Table II.)

166. F.; 16; June 1926; oedema + +; I. P. 124 days; slight oedema, albumin 10 grams per litre on discharge; died Nov. 1928. (Not included in Table II.)

181. M.; 20; Feb. 1927; oedema + +; I. P. 48 days; oedema increased; died. (Not included in Table II.)

205. M.; 39; May 1928; 'influenza'; oedema +; I. P. 16 days; no oedema, trace albumin on discharge; recurred 1928; died Nov. 1928.

245. F.; 14; Dec. 1929; scarlet fever; oedema +; convulsions, vomiting, blood non-protein nitrogen 93 mg. per 100 c.c.; indican negative; died on day of admission. (Not included in Table II.)

Group 3. Well.

7. M.; 5; Apr. 1927; nasal discharge and suppurative otitis media; oedema +; I. P. 16 days; negative on discharge; drainage of antra, and adenoids removed Sept. 1927; negative 1932.

69. M.; 4; May 1924; oedema +; I. P. 40 days; no oedema, trace albumin on discharge; recurred 1926 and 1927; tonsillectomy 1928; negative 1932.

108. M.; 19; Feb. 1925; tonsillitis; oedema +; I. P. 41 days; negative on discharge; operation for adenoids, and on nasal septum 1927; negative 1932.

124. M.; 21; May 1926; tonsillitis; oedema +; I. P. 23 days; trace albumin on discharge; recurred 1926 twice; tonsillectomy; well till alveolar abscess 1928, haematuria, tooth removed; negative 1931 and 1932.

131. F.; 7; June 1926; oedema +; I. P. 42 days; trace of blood and albumin, oedema of eyelids, on discharge; recurred 1928; tonsillectomy 1930; negative 1932.

134. F.; 16; July 1926; chronic tonsillitis; oedema +; I. P. 32 days; trace of albumin and blood on discharge; recurred three times between discharge and readmission March 1927; tonsillectomy April 1927; no further recurrence; negative 1932.

191. M.; 36; Jan. 1928; quinsy; oedema +; I. P. 34 days; negative on discharge; tonsillectomy March 1928; negative 1932.

203. M.; 11; Jan. 1928; chronic tonsillitis; oedema +; I. P. 30 days; tonsillectomy during admission; negative on discharge and 1932.

207. M.; 28; Feb. 1928; chronic tonsillitis and otitis media; oedema + +; I. P. 34 days; tonsils and adenoids removed; no oedema; trace albumin on discharge; negative 1932.

216. F.; 9; April 1928; chronic tonsillitis and bronchitis; oedema + +; I. P. 35 days; negative on discharge; recurred Aug. 1928; tonsillectomy Sept. 1928; negative 1932.

224. M.; 14; June 1928; chronic tonsillitis; oedema +; convulsions; I.P. 27 days; tonsils and adenoids removed; negative on discharge; negative 1931, accepted for Royal Marines; not seen 1932.

226. F.; 4; July 1928; tonsillitis and otitis media; oedema +; I.P. 59 days; tonsillectomy; negative on discharge, and 1932.

233. F.; 17; Oct. 1928; tonsillitis; oedema +; I.P. 46 days; tonsils and adenoids removed; trace albumin only on discharge; negative 1932.

234. M.; 13; Dec. 1928; tonsillitis; oedema ++; I.P. 66 days; tonsillectomy; no oedema, but albumin present on discharge; negative 1932.

236. M.; 7; Oct. 1928; tonsillitis; oedema +; I.P. 68 days; negative on discharge; tonsillectomy 1929; negative 1932.

244. M.; 7; Dec. 1929; chronic tonsillitis; oedema +; I.P. 29 days; tonsillectomy; negative on discharge; negative 1932.

247. F.; 13; Dec. 1928; tonsillitis; oedema +; I.P. 41 days; tonsillectomy; negative on discharge; negative 1932.

253. F.; 9; Dec. 1929; chronic tonsillitis; oedema +; I.P. 25 days; negative on discharge; tonsillectomy April 1930; negative 1932.

254. F.; 16; Apr. 1929; tonsillitis; oedema ++; I.P. 44 days; tonsillectomy; no oedema, albumin present, blood trace on discharge; negative 1932.

257. M.; 15; Nov. 1929; quinsy; oedema ++; 20 convulsions; I.P. 44 days; negative on discharge; tonsillectomy one month later; negative 1932.

258. M.; 15; Oct. 1929; tonsillitis; oedema +; I.P. 21 days; tonsillectomy; negative on discharge and 1932.

259. M.; 29; June 1929; tonsillitis; oedema +; I.P. 40 days; tonsillectomy; trace albumin only on discharge; negative 1932.

Group 3. Died.

13. M.; 43; Oct. 1927; oedema ++; tonsillitis 27.11.27; tonsillectomy 14.12.27; I.P. 82 days; oedema never entirely cleared, albuminuria ++ on discharge; readmitted Oct. 1928, oedema ++; died of pneumonia. (Not included in Table II.)

Group 4. Well.

17. M.; 9; May 1927; tonsillectomy one month ago; oedema +; I.P. 46 days; negative on discharge and 1932.

220. M.; 7; Aug. 1928; tonsils and adenoids removed three weeks before nephritis; oedema +; I.P. 18 days; trace of blood and albumin on discharge; negative 1932.

Group 4. Ill.

252. M.; 9; March 1929; mastoiditis L. (operation); oedema +; I.P. 62 days; otitis media R.; no oedema, albumin present on discharge; recurred 1929 and 1930; albumin present, blood-pressure 140, no discharge from ear, tonsils negative 1932.

Not included in either Table.

190. F.; 11; Jan. 1928; tonsillitis; oedema +, later + + +, albumin 12-20 grams per litre, empyema drained, oedema and albuminuria cleared;

I. P. 134 days; negative on discharge; readmitted 21 days later, pneumococcal meningitis, albuminuria (15 grams), oedema ++, died. The case illustrates the remarkable recovery after removal of sepsis (empyema) but the return of a septic process (pneumococcal meningitis) with recurrence of the nephritis.

225. F.; 6; Sept. 1928; tonsillitis; oedema +; I. P. 18 days; tonsillectomy; negative on discharge; Nov. 1928 oedema recurred, urinary infection (*B. coli*) found, negative 1932 except for bacilluria.

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CUTANEOUS REACTIONS IN ACUTE RHEUMATISM¹

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SINCE the work of Poynton and Paine (1) at the beginning of this century, many arguments for and against the association of streptococcal infection and acute rheumatism have been put forward by different schools. In recent years a new approach to the study of disease has been opened up by the investigation of the cutaneous reactions to bacteria. The skin reactions of rheumatic patients to streptococci and their products have been described by numerous American writers.

Birkhaug (2) found a type of non-methaemoglobin-forming streptococcus in the throats of many rheumatic subjects. From this organism he prepared a broth filtrate with which he performed a number of skin tests on acute rheumatic patients and controls. Using 0.1 c.c. of a 1/100 dilution he found that 85 per cent. rheumatic children gave positive results, while 11 per cent. of control children reacted. He found that intramuscular injection of the toxic filtrate in man and animals produced a circulating antitoxin. He followed up this line of investigation using different autolysates, filtrates, and bacterial suspensions from different types of 'green' and gamma streptococci, and found in 188 rheumatics and 408 controls that 68 per cent. of the rheumatics and 14 per cent. of the controls gave positive reactions. He stated that these filtrates were heat-labile and neutralizable, but later withdrew this statement after Swift, Derick, and Hitchcock (3) had reported stronger reactions with boiled than unboiled filtrates.

Kaiser (4) confirmed Birkhaug's findings on 801 children, from birth to sixteen years of age, with a filtrate obtained from Birkhaug's laboratory. He found that 72 per cent. rheumatics and 20 per cent. controls reacted. Irvine-Jones (5) obtained a number of streptococci of all types from the throats of rheumatic and non-rheumatic subjects and obtained filtrates from them. With these she performed a large number of skin tests on rheumatic patients and controls. The filtrates of the streptococci obtained from rheumatic patients were not more toxic than those from non-rheumatic subjects, and a considerable variation in the capacity of streptococci to produce 'toxin' was noted. Grouping the results together she found that 22.8 per cent. rheumatics and 12.7 per cent. controls gave positive reactions. Sensitivity appeared most marked during the active phase of rheumatic disease,

¹ Received June 15, 1932

though fulminating cases tended to go negative during their most acute period. It was also observed that negative cases contained a circulating antitoxin. From this result it would appear that Irvine-Jones (5) filtrates contained exotoxins similar in biological characteristics to the Dick toxin.

Swift, Wilson, and Todd (6) carried this work forward by a number of careful investigations, using filtrates from several non-haemolytic types of streptococci, and showed (a) that rheumatic patients gave a higher percentage of positive reactions than normals, (b) that active cases of rheumatic fever gave a higher proportion of positives than inactive cases, (c) that there was no relation between the capacity of patients to give skin reactions to Dick toxin and to filtrates of non-haemolytic streptococci, (d) that the reactions did not appear specific to the organism used, (e) that boiled filtrates gave as strong reactions in rheumatic cases as unheated filtrates. From these observations it seems probable that these workers were not using exotoxins akin to the Dick toxin, but some other heat-stable product of the organism. This was further borne out by the fact that in another investigation Swift, Derick, and Hitchcock showed that if 'nucleo-proteins' were used similar results were obtained. 'Nucleo-proteins' from haemolytic streptococci were observed to give more frequently positive and larger reactions on rheumatic patients than those from non-haemolytic types.

A number of animal experiments by Swift and his co-workers (10) showed that rabbits could be sensitized to non-haemolytic streptococci by the repeated injection of small doses of the organism either intradermally or subcutaneously, and that this sensitivity could be maintained by the production of an artificial focus of infection, e.g. by an infected agar tumour.

Mackenzie and Hanger (7) obtained a substance from a number of pathogenic bacteria by alkaline extraction of the ground-up bacterial bodies, which they called 'intracellular antigen'. These extracts were used for intradermal tests without appreciable dilution and many severe reactions were obtained. They found that age played an important role in determining the reaction; in young children few reactions were obtained, but with increasing age the reactions tended to become more and more severe and appeared somewhat analogous to the tuberculin reaction. They did not find any relation between streptococcal skin sensitivity and disease. The latter observation can partly be explained by the strength of the solutions used. In our experience with similar extracts, if these are used undiluted, reactions can be obtained in almost all individuals except young children and infants, as is the case with tuberculin. Indeed, in our opinion the value of all these tests depends very largely on the strength of the inoculum used, and much of the confusion in the literature is due to the fact that the potency of the preparations used by different workers is not numerically comparable. Furthermore, there is no uniformity among workers as to what shall constitute a 'positive reaction', and therefore it is misleading simply to divide cases into positive and negative reactors, without indicating the degree of positivity.

Some experiments undertaken by one of us (W. R. F. C.) some years ago, but never published, may be mentioned here as germane to this discussion: a large number of filtrates (some 30-40) of viridans and gamma streptococci were obtained by growing the organisms in Douglas's tryptic broth and Hartley's broth. The organisms used were obtained from the throats or blood of rheumatic cases, and from the blood of patients with infective endocarditis, as well as some well-known 'rheumatic' strains such as R.F. 1B. and R.F. 18, kindly supplied by the Lister Institute. Several examples of streptococcus viridans, which did not appear to autolyse on culture, gave strong filtrates which could be used at dilutions of 1/100, and one gamma streptococcus, which almost completely autolysed, produced a potent filtrate in a dilution of 1/1000. Dr. Birkhaug also very kindly sent us a couple of his own filtrates.

On testing those filtrates which contained a toxic substance on susceptible individuals, no very clear result was obtained. It was true that if grouped together rheumatic subjects gave a higher percentage of definitely strong reactions than normals, but when examined in detail the actual reactions were hard to explain. For instance, it was a common observation when two similar rheumatic cases were tested with two potent filtrates obtained from different organisms, that while one was positive to the first and negative to the second, the reverse was observed in the second case.

On the whole the viridans organisms did not appear to autolyse on prolonged culture, nor could they be artificially autolysed by the method of rapid freezing and thawing; the non-methaemoglobin-forming group, however, tended to autolyse freely if cultured in Hartley's broth for four to seven days, and could also be autolysed by heat and cold.

These and other observations, together with a study of the literature up to this date, seemed to indicate that two separate types of toxic substances were producing reactions in these skin tests. One was a heat-stable, non-neutralizable breakdown product of the organism, the other a heat-labile, neutralizable exotoxin akin to the Dick toxin. On this hypothesis it may be assumed that while Swift and his co-workers and Mackenzie and Hanger were employing the former type of toxin, though obtained by different processes, Irvine Jones was using the latter, and Birkhaug and ourselves a mixture of the two.

It was at this stage in the investigation that we became aware of the importance of the haemolytic streptococcus as an aetiological factor in rheumatic fever, while working on the epidemiology of the disease at the Cheyne Hospital. At this hospital an epidemic of tonsillitis followed by one of acute rheumatic relapses occurred during the autumn of 1930. The throat infection spread from patient to patient, and was followed in almost every case by an acute rheumatic relapse after a silent period of ten to twenty days. The organism causing the tonsillitis was the haemolytic streptococcus. An extract from the ground-up bodies of this organism was prepared with the co-operation of Dr. F. Griffith of the Ministry of Health, and this substance (which we termed an 'endotoxin') was found to give

very strong reactions when injected intradermally into rheumatic cases. Among the group of twenty-two rheumatic patients at the Cheyne Hospital, fifteen gave extremely large reactions, and seven mildly positive reactions, while only seven out of twenty controls reacted at all. This extract was shown to be heat stable and distinct from haemolytic exo-toxin (the Dick toxin). The latter gave only two positive reactions when tested on the Cheyne group of patients. A full report of the epidemic has been published elsewhere (8, 9).

The reactions obtained with this haemolytic streptococcal extract were very definite, and much more marked than those given by the filtrates of non-haemolytic streptococci already referred to above. Cases tested in other hospitals in London have confirmed these findings, and other similar epidemics have been observed. Meanwhile the importance of the haemolytic streptococcus in relation to rheumatic fever has been rapidly gaining ground elsewhere. Swift (10) has observed that a high percentage of rheumatic patients are sensitive to nucleo-protein from haemolytic streptococci, and he is treating rheumatic patients by intravenous vaccination with haemolytic streptococci. While we were making our observations at the Cheyne Hospital, Coburn's (11) book, which appeared in January 1931, was in the press. His findings are in agreement with our views in incriminating the haemolytic streptococcus as the infective factor in acute rheumatism. He devotes a chapter to the skin reactions of acute rheumatic patients to haemolytic streptococcal nucleo-protein and shows that 99 per cent. of active rheumatic patients and 95 per cent. of patients who had suffered from recent haemolytic streptococcal infection are sensitive to this substance, while in a miscellaneous group of 120 people of different ages in the medical wards of the Presbyterian Hospital, New York, only 36 per cent. were positive. He found that the degree of sensitiveness was very much greater in the rheumatic group. However, as many cases in which no rheumatic stigmata could be found gave strongly positive reactions, he concluded that a positive reaction did not in itself denote the rheumatic state, but that the high percentage of strong reactions in rheumatic patients was evidence of the association of haemolytic streptococcal infection and active acute rheumatism. He also showed that when rheumatic subjects were removed from an environment where haemolytic streptococcal infection was indigenous, signs of active rheumatic disease soon disappeared, the organism could no longer be isolated from their throats, and their skin lost its sensitivity; but on their return to their previous environment the organism tended to reappear in their throats, followed by renewed rheumatic activity and skin sensitivity.

In April, 1931, Derick and Fulton (12) reported the results of reactions obtained with 'nucleo-proteins' of haemolytic and viridans streptococci in a group of 670 individuals. They found that the haemolytic streptococcal nucleo-proteins produced very much stronger reactions than viridans nucleo-proteins. They also showed that age played an important role in deter-

mining this sensitiveness up to the age of fifteen years; after this, it ceased to influence the reactivity of the individuals tested. They found a high degree of sensitiveness to these antigens in many conditions, but most marked in active acute rheumatic disease.

Present Investigation.

The present investigation was undertaken with a view to elaborating and confirming our previous observations with haemolytic streptococcal 'endotoxin', at the Cheyne Hospital, on a larger series of cases, and at the same time ascertaining whether any analogy existed between the cutaneous reactions to this haemolytic streptococcal extract and to similar products of non-haemolytic streptococci and other pathogenic bacteria.

Methods. A. The preparation of extract ('endotoxin') from haemolytic streptococci. The organisms were cultured in 50 c.c. of glucose phosphate broth for twenty-four hours. This culture was then tipped into a litre flask of the same medium, which was incubated a further twenty-four hours, when it was centrifugalized. The deposit thus obtained was washed three times with sterile physiological salt solution, a further washing being given with sterile distilled water. After washing, the deposit was suspended in 3-4 c.c. of sterile distilled water, and the organisms killed by heating at 60° C. for fifteen minutes in a water bath.

They were then pipetted into a watch-glass and desiccated *in vacuo* for forty-eight hours, using phosphorus pentoxide as a dehydrating agent. The dried organisms were then scraped off the watch-glass and 50 mg. placed in a ball mill and the organisms ground for forty-eight hours. Twenty c.c. of carbol-saline were now added and well mixed with the ground organisms. This suspension was then centrifugalized and the supernatant fluid which contained the 'endotoxin' collected (if the grinding operation has been properly carried out a gram-stained film of the deposit should show no gram-positive organisms, the residue consisting of a mass of gram-negative cell membranes and debris). The nitrogen content of the fluid was then estimated.

The standard extract concentrated solution was made up to contain 10 mg. of nitrogen in 100 c.c. and was stored on ice. Dilutions of 1/250 and 1/500 for actual use were made from this standard, and 0.1 c.c. of these dilutions used for intradermal tests.

In our previous communications we have referred to the soluble ground-up extract of the organism as 'endotoxin'. The American school, using an acid precipitate of a similar extract, have termed their product 'nucleo-protein'. The active principle in both these preparations is, we believe, identical, but both names are somewhat unsatisfactory owing to our present incomplete knowledge of their composition and properties. We shall refer to the substance in this report as haemolytic streptococcal extract (or H.S.E.).

B. Method of performing and reading skin tests. The method used is similar to that employed for the Mantoux tuberculin test: 0.1 c.c. of the

extract is introduced between the layers of the skin by means of a fine short bevelled needle, and the result read after twenty-four hours.

In the present investigation two dilutions of our standard H.S.E. (10 mg. N₂ per 100 c.c.) were used (1/250 and 1/500 dilutions) in every case, and the reaction of the patient was judged by a reading of the two considered together. The extracts from other organisms were all found to be considerably less potent than H.S.E., and were used only in dilutions of 1/250 and 1/100. The reactions to H.S.E. were divided into three main groups (1) negative, when there was no reaction at the site of the 1/500 test, and less than 10 m.m. erythema without oedema at the site of the (1/250) injection, (2) border-line '±' when there was less than 10 m.m. erythema at the 1/500 site, and only a slight reaction at the 1/250 site without oedema, (3) strongly positive, when oedema and erythema were present, but the site of the 1/250 inoculation showed a stronger reaction than at the 1/500 site; (4) very strongly positive when the reaction was so intense that the different dilutions made no difference, and the reaction was the same at both the 1/500 and 1/250 sites.

We realize that this method is entirely arbitrary, and hence the terms 'positive' and 'negative', without any qualification, are hardly applicable to the readings. No laboratory animal was found suitable for the standardization of the extract, hence the rough method described above had to be used. The strength of the standard used was chosen after considerable experiment, and study of the literature. It was made intentionally less potent than Coburn's 'nucleo-protein' as we were anxious to avoid severe reactions in very sensitive cases. Hence his figures cannot be accurately compared with ours, though his results taken generally form a reasonable basis of comparison.

The interpretation of results is difficult, due to a number of variables. Skins vary greatly in their capacity to react, some reacting violently to all inocula to which the patient is sensitive, others only slightly. The actual amount of inoculum introduced into the skin may vary, as in performing the test it is sometimes difficult to avoid introducing some of the material subcutaneously as well as intradermally. In some cases the skin lymphatics are directly injected, leading to a wider dissemination of the inoculum. Also the general condition of the patient is a factor of great importance. Acutely ill patients, from whatever cause, lose all skin reactivity, and in those with chronic wasting disease associated with emaciation, heart failure, &c., the skin reactivity is much reduced. This phenomenon is, we believe, merely a non-specific failure on the part of the cutaneous cells to react. A similar phenomenon has been observed by Swift in 'cachectic' rabbits. Patients with long-standing carditis have tended to fall into this group, and their reactions have been particularly hard to interpret. This type of tissue reaction is as yet but partially understood, hence we have endeavoured to give the complete detail of the methods used, so that other workers may be able to evaluate the actual results reported.

Results

In the present investigation the skin reactions of 303 rheumatic children have been tested to H.S.E., while 256 non-rheumatic children have been similarly examined to serve as a control. The rheumatic children were drawn from the rheumatic clinic at the Hospital for Sick Children, Great Ormond Street, from Queen Mary's Hospital, Carshalton, the Cheyne Hospital for Children, and the Lancing Rheumatic Convalescent Home, while the control children were in the surgical wards of the Hospital for Sick Children and Queen Mary's Hospital, Carshalton. Among the controls were many cases of recent acute infection such as otitis, mastoiditis, osteomyelitis.

The rheumatic series consisted of children who were at the time suffering from, or had previously suffered from, polyarthrititis, carditis, or chorea. Children whose only claim to rheumatism consisted of vague limb pains (so-called subacute rheumatism) have not been included, but are mentioned later in a separate group.

TABLE I

Intradermal Reactions to Haemolytic Streptococcal Extract, using 0.1 c.c. of 1/250 and 1/500 Dilutions

	Strongly positive reactions.	Borderline (\pm) reactions.	Negative reactions.
303 rheumatic children	176 58 %	51 17 %	76 25 %
256 non-rheumatic children	71 28 %	48 19 %	137 53 %

The results are set out in Table I. Of the 303 rheumatic children, 58 per cent. reacted strongly, while of the 256 control children 28 per cent. gave definitely positive reactions. Border-line reactions (indicated by the sign \pm) occurred in 17 per cent. of the rheumatic children, and in 19 per cent. of the controls, while 25 per cent. of the rheumatic children and 53 per cent. of the controls failed to give any reaction.

These results indicate that rheumatic children give a considerably higher percentage of definitely positive reactions to H.S.E. than do non-rheumatic children.

During this investigation it was our impression that the largest reactions were likely to be obtained from children suffering from chorea. By separating the 303 rheumatic children into those with chorea and those with carditis but without chorea, it was found that strongly positive reactions were obtained in 64 per cent. of the cases of chorea and in 54 per cent. of the cases of carditis. Choreic children would thus seem to be slightly more sensitive to H.S.E. than children with carditis.

From the preceding analyses two points call for comment. In the first place a quarter of the rheumatic children failed to give a reaction to the haemolytic streptococcal extract, and in the second place a little over a quarter of the non-rheumatic children gave strong positive reactions.

It seemed to us probable that some of the negative results among the rheumatic children were due to the long interval that had elapsed since the last acute rheumatic manifestation, and accordingly the cases were tabulated from this point of view. The results are set out in Chart I, from which it will be seen that approximately 80 per cent. of rheumatic children give strong positive reactions for a period up to six months after their last acute attack—whether this be in the form of chorea, carditis, or poly-

CHART I

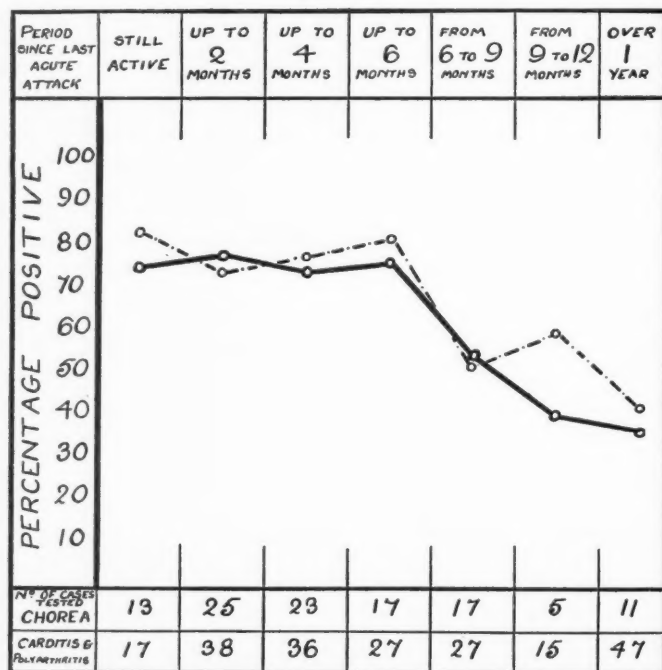


Chart I. Skin reactions to H.S.E. according to period of time elapsing since last acute rheumatic attack (fulminating cases excluded).

Continuous line. Cases of chorea only.

Broken line. Cases of carditis and polyarthritis without chorea.

arthritis. The number of positive cases falls to 40 per cent. at the end of a year from the time of the most recent rheumatic attack, and thereafter remains at about that figure. It will be shown later that between the ages of 10 and 12 years the number of strong reactions among the control children reaches approximately 40 per cent., which may have some bearing on the fact that the number of rheumatic children who react positively does not fall below about 40 per cent. even when three or four years have elapsed since their last acute attack.

Influence of age. The influence of age in determining skin reactivity among the control children was next investigated, and the results are shown

in Chart II. The lowest curve shows the percentage of strong positive reactors among the control children according to age, and it is seen to rise in an almost straight line up to twelve to fourteen years, after which it ceases to rise. It would appear that in the non-rheumatic child, age plays an important role in producing positive reactions to H.S.E., an observation which is in accord with the findings of Mackenzie and Hangar, and Derick and Fulton. The latter observers have also pointed out that the likelihood of positive reactions does not increase with age after fourteen years.

CHART II

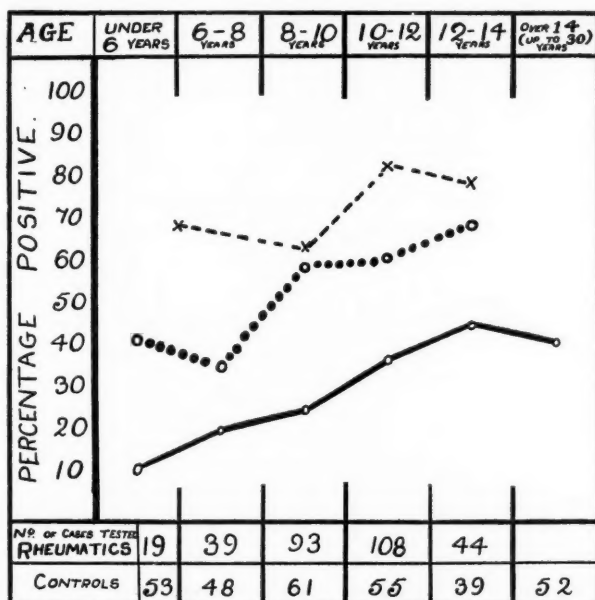


Chart II. Skin reactions to H.S.E. according to age groups.

Unbroken line. Non-rheumatic cases.

Dotted line. Rheumatic cases.

Broken line. Active and recently active rheumatic cases (within six months of last attack).

It is of interest to note that the increase of reactivity to haemolytic streptococcal extract during the years of childhood runs parallel with the age curve for the intracutaneous tuberculin test in clinically non-tuberculous subjects, as given by D'Arcy Hart. His figures are given in the following table.

TABLE II²

Intracutaneous Tuberculin Test on 751 Clinically Non-Tuberculous Controls (using 0.1 c.c. of 1/1000 Tuberculin)

Age.	0-2 years.	3-5 years.	6-10 years.	11-20 years.	over 21 years.
Percentage Positive	6.5	17	30.5	60.5	88

² With permission from Dr. D'Arcy Hart (13).

Although the tuberculin and the H.S.E. age curves run parallel in childhood, they differ in later life in that while the number of tuberculin-positive cases continues to increase, the streptococcal-positive cases do not increase in numbers after about the fourteenth year.

In Chart II the middle curve represents the percentage of strongly positive rheumatic children according to age, and is seen to rise with age in a somewhat parallel line to that of the control children (lowest curve), though on a higher level. But when a curve is drawn representing only active cases, and those in which an acute attack has occurred not more than six months before the test, this apparent analogy disappears. The top curve represents these active and recent cases, and is seen to run a somewhat irregular course, but only shows a 10 per cent. increase in strongly reacting patients between the youngest and oldest age groups.

Fulminating cases. Early in the investigation it was noticed that acutely ill children failed to show any trace of skin reactivity, either to H.S.E., tuberculin, Dick toxin, or other bacterial product. This failure to react was noted in all of thirteen cases of severe acute carditis. In several of these cases the skin reactions to H.S.E. had been done before the acute rheumatic attack, and had been noted as strongly positive, while a positive reaction was also observed to return as the children recovered.

A modified reaction was also observed in children suffering from cardiac failure with orthopnoea, and ascites or oedema of the feet. In these patients, oedema was seldom seen at the site of inoculation, and the surrounding erythema was faint. Failure to react under these circumstances seemed to us to indicate a simple inability of the cutaneous cells to produce a reaction, and not to be regarded as a specific phenomenon.

Relation to Dick test. In our previous report (*Lancet*, 1931, 2, 1341) we stated that rheumatic children showed no correlation between their reaction to haemolytic streptococcal exo-toxin (the Dick toxin) and 'endotoxin' (H.S.E.). This has been repeated on a larger scale, and the results, set out in Chart III, give confirmation to our earlier report. In individual cases it was found that a positive reaction to H.S.E. gave no indication of what the Dick test might be, and vice versa. Taken in larger numbers, as in Chart III, it will be seen that after the age of six to eight years, the percentage of Dick positives steadily diminishes, while the number of cases positive to H.S.E. continues to increase.

Reactions to viridans and gamma streptococci. Extracts from two types of viridans and one type of gamma streptococcus were made in a similar manner to H.S.E. The viridans streptococci were obtained from the throats of two rheumatic patients at the Cheyne Hospital, and the gamma type from a normal throat with the help of Dr. D. Thomson of the Pickett-Thomson Research Laboratory, who regarded it as similar to the type described by Birkhaug.

On testing these extracts on a number of children it was found that only one of the viridans strains produced a 'toxic' extract. The gamma strain produced a more potent extract than the active viridans strain, but both

were much less potent than similar haemolytic extracts. In the tests with these extracts dilutions of 1/250 and 1/100 were used, as higher dilutions failed to produce any reactions.

A large number of tests were performed with the two potent extracts (viridans and gamma), and H.S.E. in rheumatic cases and controls, to ascertain whether the active principle which is found in H.S.E. is identical to that in extracts from these non-haemolytic types of streptococci, and whether rheumatic patients are more sensitive to these extracts than controls. No correlation was found in the reactions of H.S.E., viridans and gamma extracts. Certain cases were found to be sensitive to all three extracts, others who were sensitive to H.S.E. were negative to the other two, while a third group of patients gave strong reactions to viridans and gamma

CHART III

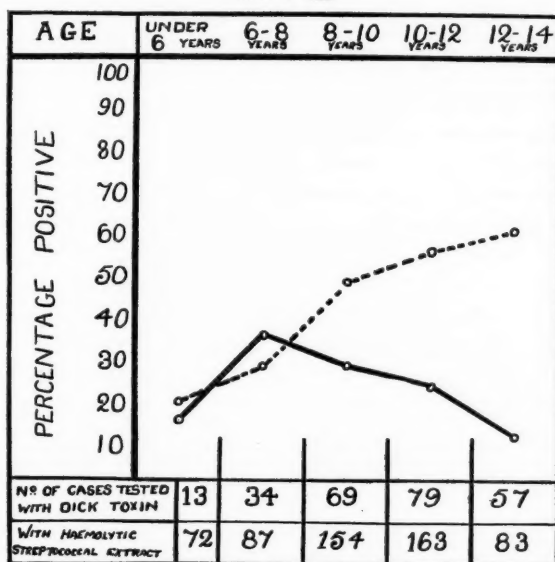


Chart III. Comparison of skin reactions to Dick toxin and H.S.E. according to age. (Rheumatic and non-rheumatic cases are grouped together.)

Continuous line. Positive Dick reactions.

Broken line. Positive H.S.E. reactions.

streptococci but not to H.S.E. This was particularly observed in two patients with Still's disease. Nor was there any correlation between the viridans and gamma extracts, some patients reacting to one and not to the other, and vice versa. Hence we conclude that the active principle causing the skin reaction in H.S.E. is distinct from that of non-haemolytic streptococci.

The reactions obtained with viridans and gamma extracts were weaker than H.S.E., and many more doubtful and border-line reactions occurred. Hence when we came to analyse our results we found we had not the necessary

statistical data to answer the question whether rheumatic patients were more sensitive to viridans and gamma extracts than non-rheumatic patients. We found, however, stronger reactions among the rheumatic patients tested to the viridans extract than among the controls, though the reverse was observed with the gamma extract.

The difference between this latter observation and the literature dealing with skin reactions of rheumatic subjects to non-haemolytic streptococcal products may be explained by our method of only considering strong reactions as definitely positive.

Skin tests with other bacterial extracts. Extracts were made by the same method as described above from *Bacillus coli*, pneumococcus, Pfeiffer's bacillus, diphtheroid bacillus, and staphylococcus aureus haemolyticus, and these were tested on some thirty patients whose reactions to H.S.E. were known. No correlation was found between the reactions obtained with these extracts and H.S.E. Many of the rheumatic patients were also tested to tuberculin and Schick toxin; again no correlation was found between those cases reacting to these substances and to H.S.E. Hence we may assume that the reaction to H.S.E. is specific and not merely an expression of general skin sensitivity.

Subacute rheumatism. For many years aching pains in the limbs have been recognized as a common precursor of acute rheumatism. It has, therefore, been assumed that muscle, tendon, and joint pains which occur in many children are symptoms of what has been called 'the subacute rheumatic state'. Since the introduction of rheumatic clinics in London these so-called subacute rheumatic patients have become a formidable problem. For instance, one-quarter of the patients transferred to the rheumatic clinic from the general out-patient department at the Hospital for Sick Children, Great Ormond Street, fall into this group, and as many as fifty of the beds allotted by the London County Council to rheumatic children at Queen Mary's Hospital are at any one time occupied by such cases. Some of these cases do not go on to frank acute rheumatism, and without doubt other causes as well as acute rheumatism exist for aching pains in the child. We have skin tested to H.S.E. 39 children, designated as subacute rheumatics, and found that only 16 gave strong reactions, 12 border-line reactions, and 11 no reactions. It is too soon to say whether this skin test is of value in helping to differentiate between limb pains due to acute rheumatism and those caused by other conditions.

Discussion

This work brings out the importance of the substance which we previously referred to as haemolytic streptococcal 'endotoxin', but here now prefer to call haemolytic streptococcal extract. The active principle in this substance is of considerable potency, but only produces a reaction in certain sensitive individuals; it is not a generally poisonous substance as are the true toxins.

It may be compared to tuberculin both in its mode of action and by certain properties, e.g. it is heat stable and probably non-neutralizable. On the other hand, the tuberculin test if once positive tends to remain positive, while in rheumatic cases a positive reaction to the haemolytic streptococcal extract tends to diminish after a period of six months from the last acute attack of rheumatism. It is quite distinct from the exotoxin produced by the same organism, as the latter (Dick toxin) can be destroyed by heat and is neutralizable by a specific antitoxin. The skin test curves of these two substances, when plotted for age, cross in the six to eight year age period (see Chart III): after this period the exotoxin curve falls steadily, while that of the extract continues to rise up to the age of puberty.

Similar extracts may be obtained from other types of bacteria, but they vary greatly in potency. Of those organisms which affect the respiratory tract the tubercle bacillus and the haemolytic streptococcus seem to contain the most potent active principles when tested intradermally. Indeed, the skin reactions to haemolytic streptococcal extract are sometimes severe. Coburn, using stronger solutions, demonstrated in the illustrations in his book how destructive these reactions could be. Although we have endeavoured to avoid bad reactions, we have observed some very striking results in certain cases, such as areas of erythema of 40–50 mm., with much oedema and some vesiculation of the centre of the reacting area.

Furthermore, one of us (14), working on erythema nodosum, was able to show that that disease was associated with great tissue hypersensitivity either to tuberculin or to haemolytic streptococcal extract. In one of the tuberculous cases the eruption was actually made to appear on the legs by the injection of tuberculin subcutaneously in the arm. In the streptococcal cases lesions resembling the true nodes of the disease were produced locally by the injection of a minute quantity of haemolytic streptococcal extract. When it is remembered that these reactions are caused by minute amounts of a substance which even in much stronger dilutions has no effect on other individuals, it will be seen that we are dealing with a type of tissue reaction as yet only partially understood, but one probably of fundamental importance in the problems of immunity.

Whether hypersensitivity to H.S.E. is acquired after any acute infection with the haemolytic streptococcus is a question of considerable importance. Tests with H.S.E. performed by us on about thirty cases of scarlet fever—a disease which we now know to be due to infection with the haemolytic streptococcus—indicate that while the skin reaction is not altered in many cases, a certain number acquire a positive reaction in the second to third week after the initial onset of the illness. At the present time a further investigation of this point is being carried out, and it is hoped to make a more detailed report later.

Taken as a whole, the results reported here are an additional link in the chain of evidence at present being forged in support of the hypothesis that haemolytic streptococcal infection plays an integral part in the aetiology of

acute rheumatism. It has been demonstrated that rheumatic children show a much greater response to haemolytic streptococcal extract than other children, and that the recentness of the last attack of acute rheumatism is an important factor in the production of the reaction.

Summary

1. A brief review of the literature concerning the skin reactions of rheumatic children to streptococcal products is given.

2. The reactions of rheumatic and non-rheumatic children to the soluble extract of the ground-up bodies of haemolytic streptococci has been investigated. The results indicate:

(a) That rheumatic children are more sensitive to this extract than are non-rheumatics.

(b) That of the rheumatic children, those with chorea are the most sensitive.

(c) That children with active acute rheumatism, and for a period of six months after the acute attack, show a high percentage of strongly positive reactions (80 per cent.). After six months this reactivity diminishes.

(d) That children with fulminating carditis lose their skin reactivity during the severe phase of their illness, though they tend to regain it later. Patients with chronic cardiac failure also tend to give much reduced reactions.

(e) That age is an important factor in determining the probability of positive reactions up to the age of puberty.

(f) That skin reactions to haemolytic streptococcal extract appear to bear no relation to skin reactions with haemolytic streptococcal exotoxin (Dick toxin).

3. A comparative study of the skin reactions of extracts of haemolytic, green and non-methaemoglobin-forming streptococci appears to indicate that these extracts do not contain a common active principle, but that each extract gives a specific skin reaction. Rheumatic children, when tested to extracts of two viridans streptococci and one gamma streptococcus, only showed a higher percentage of strongly positive reactions to one of the viridans extracts than did the controls.

4. Skin reactions of rheumatic children to tuberculin, Schick toxin, and extracts from pneumococci, staphylococci, diphtheroid bacilli, and Pfeiffer's bacillus, do not show a higher sensitivity than do non-rheumatic children, and thereby differ from the skin reactions produced by haemolytic streptococcal extract.

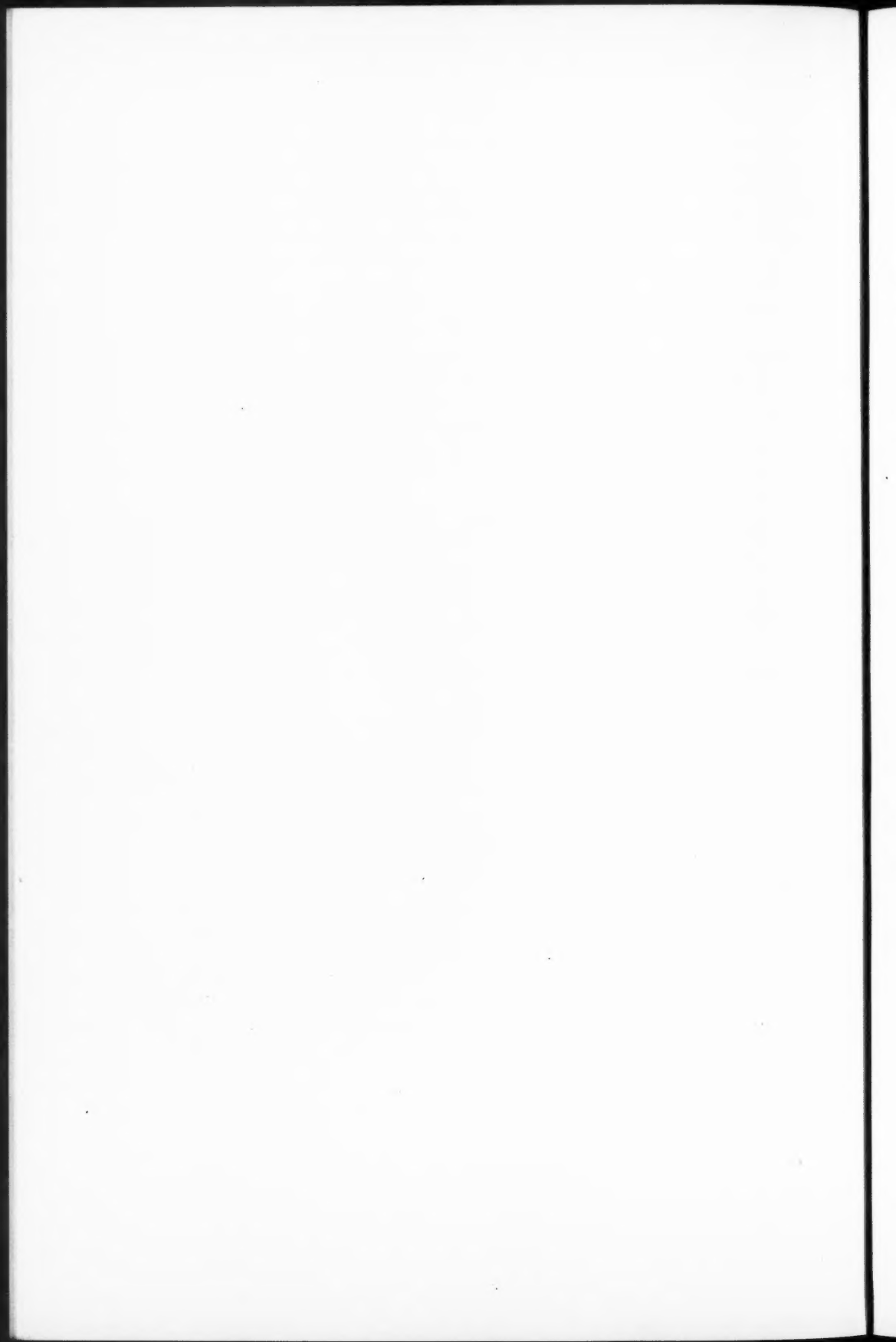
We wish to express our thanks to the Medical Staff of the Hospital for Sick Children, Great Ormond Street, and the London County Council for the facilities which have been granted to us in this investigation. We are particularly grateful for the encouragement given us by Dr. Nabarro and

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ALKALOSIS OCCURRING IN THE ALKALINE TREATMENT OF PEPTIC ULCERS¹

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Introduction

THE toxic effects of large doses of sodium bicarbonate, especially when given to patients with impaired renal function, are well known. Many cases of uncompensated alkalosis and tetany have been reported resulting from doses of from 150 to 200 grm. by the mouth and from 25 to 60 grm. intravenously. The alkalosis sometimes occurring in the alkaline treatment of peptic ulcer follows the use of much smaller amounts of sodium bicarbonate, of the order of 10-50 grm. per diem, and clearly cannot be classed as mere overdosage.

The first systematic and intensive use of alkalis in gastric disease dates from Sippy's paper in 1915, and although he observed some—as then unexplained—symptoms of dizziness and malaise in some of his patients, no published report of his cases was made until Gatewood, 1925, quoted Frazier, who, working in Sippy's clinic in 1918-19, found values for the CO₂ combining power of the plasma above 80 vols. per cent. in 17 per cent., and above 100 vols. per cent. in 6.25 per cent. of the cases studied. The first full account of uncompensated alkalosis following the Sippy treatment was that of Hardt and Rivers, 1923, who reported sixteen cases, and their excellent clinical description has had little added to it by subsequent writers. They found that toxic symptoms came on from four days up to four weeks after the commencement of treatment, sometimes appearing while the gastric acidity was still high and before the urine had become alkaline. Their patients were introspective, irritable and nervous, with a distaste for food (especially for milk), headache, nausea, vomiting, dizziness, and aching in the trunk and limbs, going on to weakness, prostration, slowness of respiration, rapid pulse, flushed face, perspiration, and drowsiness. Chemical examination of the blood showed a raised CO₂ combining power of the plasma and a raised urea and creatinine content in all cases, while some cases had protein, pus, and casts in the urine. One fatal case showed *post mortem* a subacute nephritis. Hardt and Rivers suspected hypochloraemia

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as a possible factor in the causation of symptoms, but in the one case where it was examined the blood-chloride was normal. They recognized the predisposing factors of ulceration near the pylorus, and renal insufficiency.

Other authors, mostly in the United States, have reported between them forty-three cases (see References 2, 8, 9, 11, 14, 15, 16, 21, 25, and 33), and the present paper reports nine, making a total of sixty-eight cases. Examination of the reports of these cases, together with other papers bearing on the subject, reveals diverse views on the incidence of 'alkalosis'. Gatewood (1925) writes: 'Alkalosis has occurred at some stage of treatment in 18 per cent. of my cases, but in only 2 per cent. has it prevented further alkaline therapy.' These figures are in accord with Frazier's, referred to above. Eusterman (quoted by Jordan) holds that if Sippy treatment is carried out indiscriminately, 25 per cent. of cases may get alkalosis. Gatewood, Gaebler, Muntwyler, and Myers also reported a high incidence—'about two-thirds of these patients at some time showed a high carbon dioxide content or pH or both, and 21 (out of 46) showed an uncompensated alkalosis, if electrometric pH values of 7.48 or above may be taken as a reliable guide'. Actually only 15 of these 21 cases were receiving alkalis, the remainder being cases of pyloric obstruction with vomiting, so the incidence may be taken as 15 out of 46, i.e. 32 per cent. Other authors, on the other hand, have found the condition to be far less common. Jordan saw 3 per cent. in her 100 cases, and Bloch and Serby 'used alkalis in the treatment of peptic ulcer for many years and have rarely seen the serious manifestations described by others'. MacLean stated that in 400 patients whom he had treated, not a single one showed any symptoms, and that altogether he had seen only two patients who showed signs of alkalosis. The nine cases reported in this paper occurred among 200 patients treated on alkaline diet, giving a case incidence of 4.5 per cent. These great variations in incidence are doubtless dependent upon the amount of alkali given; in MacLean's cases and in those reported in this paper the patients rarely received more than the equivalent of 10 to 15 gm. of sodium bicarbonate per diem, whereas the usual American practice is to increase the dose until the gastric acidity is neutralized, so that Gatewood's patients, for example, received on an average 50 to 65 gm. daily, and as much as 130 to 160 gm. in refractory cases.

Cases have been reported at ages from 24 to 75, with an average of 44 years, and males predominate over females in the ratio of 2:1. Among the 68 cases collected above there were three deaths from alkalosis—4.4 per cent. In the 55 cases where the site of the ulcer was specified, there were 37 duodenal ulcers (67.3 per cent.), 17 gastric ulcers (30.9 per cent.) and one jejunal ulcer (1.8 per cent.). In 12 cases pyloric obstruction was stated as being present, in 28 it was stated as being absent. In the remaining duodenal and pyloric ulcer cases it can probably be assumed that there was no appreciable obstruction, from the recovery of the patients when the alkalis were discontinued.

Cases

During two years about 200 in-patients were treated with the alkaline diet in the Medical Unit Wards at St. Thomas's Hospital. A close watch was kept on these cases for any untoward symptoms, and any cases showing such symptoms were investigated clinically and chemically to determine the cause. Fifteen cases were investigated, and nine showed the characteristic changes of 'alkalosis'. The six cases with normal blood-findings had all been on alkalis from five to twelve days.

Methods. Blood was withdrawn from a vein, without stasis, into a 20 c.c. Record syringe containing 40 mg. of potassium oxalate (i.e. 2 mg. per cc. of blood), immediately mixed and cooled under running water to room temperature. In two patients the pH was determined at room temperature by the electrometric method, using the glass electrode described by Kerridge. The patient's temperature and the room temperature were noted, and the correction applied was that suggested by Havard and Kerridge, viz. 0.015 pH subtracted from the room-temperature reading for each degree centigrade of difference. The pH determinations were done within four minutes of the withdrawal of blood. Estimation of the whole blood pH in eleven normal persons by the technique described above gave readings from 7.25 to 7.40, with an average of 7.34. These figures are in accord with Millet's findings by the same method. Half of the remaining blood was then introduced, under paraffin, into a centrifuge tube and the plasma separated. The CO_2 combining power of the plasma was estimated by Van Slyke's method (1917). The total non-protein nitrogen and urea nitrogen of the whole blood were determined by the methods of Folin and Denis and Marshall and Van Slyke respectively; the inorganic phosphorus of whole blood and of plasma by Fiske and Subbarow's method, and the chloride (as NaCl) by Van Slyke's method (1923). The urine was collected in 24-hourly specimens, preserved with toluol, the total nitrogen determined by Kjeldhal's method, the urea by the hypobromite method, the phosphorus (as P_2O_5) by Fiske and Subbarow's method, and the chlorides (as NaCl) at first by Volhard's and later by Van Slyke's method. The Volhard method was discarded because it was found to be less accurate.

The total amount of alkalis in the diet which these patients were given was:—

Sodium bicarbonate (soluble)	7.2	gram. daily
Heavy magnesium carbonate (insoluble)	7.2	" "
Prepared chalk (insoluble)	7.2	" "
Bismuth oxycarbonate (insoluble)	18.0	" "
Sodium citrate (soluble)	12.0	" "
Magnesium hydroxide (insoluble)	1.0	" "

Oxidization of the sodium citrate by the body yields 3.5 gram. of sodium bicarbonate, so that the total amount of *soluble alkali* is equivalent to 10.7 gram. of sodium bicarbonate daily.

Case 1. Female, aged 45 years. This patient was an undersized woman of poor physical development, with a very gross kypho-scoliosis which she had had since childhood. For fourteen years she had suffered from symptoms suggesting an ulcer at the pylorus. Physical examination and a barium meal confirmed the diagnosis and showed some pyloric obstruction. After five days of alkaline diet she complained of headache, backache, an unpleasant taste in the mouth, a feeling of being cold and of passing an excessive volume of urine. Physical examination showed no new signs. The urine was strongly alkaline, but otherwise normal and a urea concentration test showed the pathologically low maximum of 1.7 per cent. After seven days of alkalis the patient looked and felt extremely ill and began to vomit. No Trousseau's or Chvostek's signs could be elicited, nor were the tendon reflexes altered, but the limb muscles were extremely excitable to the stimulus of light tapping. Alkalis were stopped and ammonium chloride given by mouth (2.7 grm. per diem). All symptoms subsided in four days.

Date.	Plasma CO ₂ vols. %	Non-protein nitrogen mg. %	Urea nitrogen mg. %	Plasma phosphate mg. %	Blood phosphate mg. %	Plasma NaCl mg. %	Blood NaCl mg. %
Mar. 19	93	63	29	5.2	4.5	566	491
Mar. 21	Alkaline treatment stopped						
Mar. 25	73	38	21	3.6	3.7	589	517
Apr. 2	86	25	16	3.9	3.8	576	512
Apr. 16	84	27	13	4.4	4.7	566	508
Apr. 23	85	35	15	4.2	3.8	566	515
Oct. 23	84	29	11	2.9	3.0	590	524

This is an unusual case where 'alkalosis' supervened in a patient with a habitually high blood bicarbonate, and is not typical. Owing to the chest deformity and consequent deficient lung ventilation, there was CO₂ retention and a compensatory rise in bicarbonate (Area 4 of Van Slyke, 1921). Scott found that the average CO₂ combining power of the plasma was 62.6 vols. per cent. in normals and 81.1 vols. per cent. in emphysematous subjects. The first figure of 93 vols. per cent. is undoubtedly pathological, the 73 vols. per cent. followed 10.7 grm. of ammonium chloride, and the remaining four readings 84-86 vols. per cent., although high, are *normal for this patient*.

Case 2. Male, aged 42 years. This patient had had a gastric ulcer and marked hyperacidity for eight years, during which time he had been treated with alkalis almost continuously, with a dosage of sodium bicarbonate varying from 10 grm. to 3 grm. daily. The first symptoms of any systemic disturbance occurred in December 1928 and January 1929, when he had headache, backache, an unpleasant taste in the mouth, vomiting, and bloodshot eyes. Recovery took place without any special treatment, and no symptoms of note occurred until September 15, when he began to have epigastric pain and vomiting. Regarding these symptoms as due to a return of gastric ulceration, he increased the dose of alkali himself, taking five heaped teaspoonfuls daily. On admission to hospital on the 24th, nine days after the onset of these symptoms, the patient looked ill, complained of epigastric pain and vomiting, had pains in the limbs, an unpleasant taste in the mouth, and, although normally of a reasonable and complacent character, was irritable and difficult to manage. The vomiting was so intense that pyloric obstruction was suspected, but no visible peristalsis was

seen. The urine was alkaline and contained protein and casts. He was put on a modified alkaline diet, receiving 5 gm. of sodium bicarbonate daily, and becoming steadily worse. By October 1, he had, in addition to the findings on admission, hiccough, headache, backache, intense thirst, bloodshot eyes, and occasionally the carpal spasms of tetany. Trousseau's and Hoffmann's signs were present, but Chvostek's sign could not be elicited.

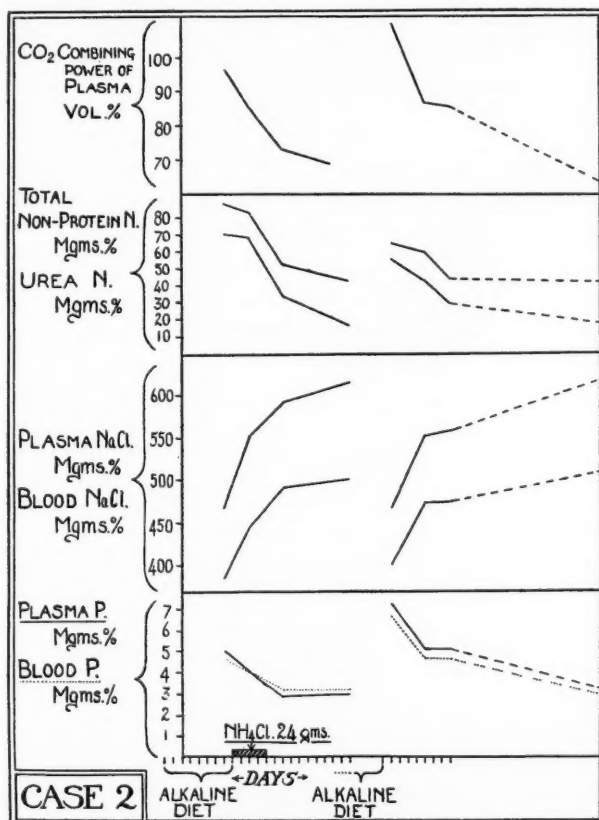


FIG. 1. The blood changes in Case 2.

Erb's sign of electrical hyperexcitability was probably present; the chronaxie could not be done, but the galvanic make and break of the right biceps was 1.0 milliampere. A urea concentration test showed the low maximum concentration of 1.25 per cent. On October 2, he was taken off alkalis and put on ammonium chloride 6 gm. daily. The tetany disappeared in twenty-four hours and all symptoms settled in seven days.

Date.	Plasma CO ₂	Non-protein nitrogen.	Urea nitrogen.	Plasma phosphate.	Blood phosphate.	Plasma NaCl.	Blood NaCl.
Oct. 1	97	90	71	5.0	4.7	468	386
Oct. 2	Alkaline treatment stopped						
Oct. 4	86	84	69	4.0	4.0	553	445
Oct. 8	73	53	34	3.0	3.2	594	492
Oct. 16	67	43	17	3.0	3.2	618	502

After the attacks had subsided, the patient was free from symptoms, without any treatment for two months. He was re-admitted on January 22, and was put on smaller doses of alkalis. On February 7, symptoms of 'alkalosis' were again manifested and the alkalis were stopped on the 13th. Recovery was slower than in the previous attack and the patient, who had been difficult to manage, discharged himself on the 21st, still with symptoms. Recovery was complete in ten days.

Date.	Plasma CO ₂	Non-protein nitrogen.	Urea nitrogen.	Plasma phosphate.	Blood phosphate.	Plasma NaCl.	Blood NaCl.
Feb. 13	Alkaline treatment stopped						
Feb. 14	110	65	56	7.2	6.7	468	401
Feb. 18	88	60	44	5.1	4.7	545	474
Feb. 21	86	45	30	5.1	4.6	558	476
May 13	63	45	19	3.2	3.0	619	510

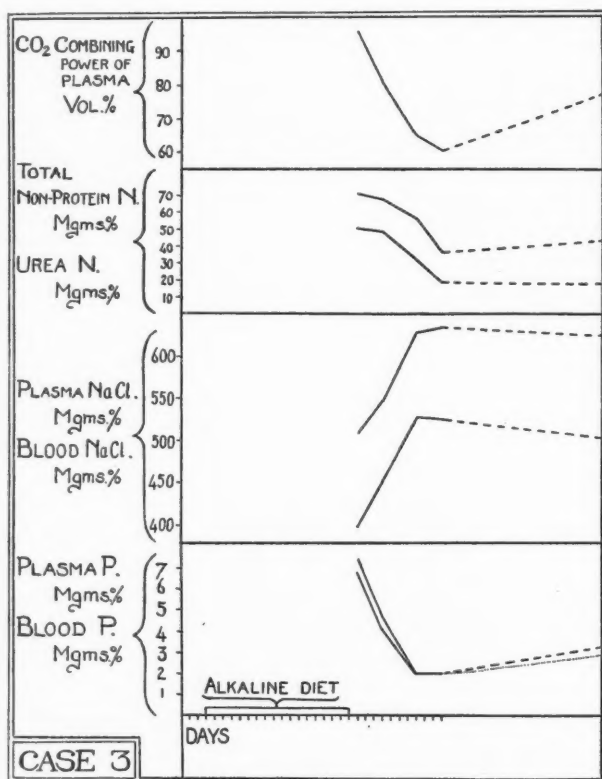


FIG. 2. The blood changes in Case 3.

Case 3. Male, aged 42 years. The patient had had scarlet fever at 12 years, but no renal complications were known. Symptoms of gastric ulcer had been present for 14 years and the following operations had been performed: gastro-enterostomy, June 1917, stoma enlarged, October 1921, adhesions divided, October 1923, pyloroplasty, September 1924. He had been on alkalis almost continuously for 2½ years. On January 20, after eleven days of intensive alkaline treatment, he began to show symptoms of

'alkalosis' and two days later had headache, dryness of mouth and throat, dizziness, nausea and vomiting, pain in the chest, pain in the eyes, and paraesthesiae of hands and feet. On physical examination he appeared extremely ill with mental irritability and proteinuria, otherwise the findings were normal. Clinical recovery was complete in three days after the alkalis were stopped. No acidotic drugs were given.

Date.	Plasma CO ₂	Non-protein nitrogen.	Urea nitrogen.	Plasma phosphate.	Blood phosphate.	Plasma NaCl.	Blood NaCl.
Feb. 24	Alkaline treatment stopped						
Feb. 25	96	71	50	7.4	6.8	510	399
Feb. 28	82	67	48	4.6	4.2	548	452
Mar. 4	65	56	32	2.0	2.0	629	527
Mar. 7	62	36	19	2.0	2.0	634	524
May 16	77	43	19	3.2	3.1	627	502

Three months after the attack, the urine was normal and a urea concentration test gave a maximum concentration of 2.45 per cent.

Case 4. Male, aged 57 years. After one year's history of intermittent dyspepsia, this man was admitted on March 29 with a perforated pyloric ulcer which was successfully sutured. Six days after operation he was put on small doses of alkalis (4 grm. of sodium bicarbonate per diem) and in three days developed symptoms of 'alkalosis'. After nine days of the diet, alkalis were stopped, and on the eleventh day he was extremely ill, semi-conscious, doubly incontinent, and, to all appearances, moribund. The urine was *acid* and contained protein and casts. The blood changes were as follows:

Date.	pH.	Plasma CO ₂	Non-protein nitrogen.	Urea nitrogen.	Plasma phosphate.	Plasma NaCl.	Blood NaCl.
Apr. 12	Alkaline treatment stopped						
Apr. 15	7.55	75	136	121	5.9	493	408
Apr. 16	7.43	76	123	104	3.8	519	449
Apr. 17	7.43	75	109	107	4.0	536	474
Apr. 19	7.47	74	91	82	4.9	563	509
Apr. 22	7.39	68	57	39	3.8	581	538
Apr. 25	7.38	65	43	26	2.9	593	541
May 9	—	64	36	19	3.3	599	534

He was treated with 10 grm. of sodium chloride intravenously and 5 grm. of ammonium chloride per rectum. Recovery was slow, taking ten days from the cessation of alkaline treatment. A fortnight after clinical recovery, a urea concentration test showed a maximum concentration of only 1.83 per cent., but nine months later had risen to 2.45 per cent.

Case 5. Female, aged 40 years. This patient had a ten years' history of gastric ulcer, which included four haematemeses and a perforation. Alkalis had been taken intermittently for the last four years without untoward symptoms, but there then occurred what the patient described as 'severe pains in the limbs and mental confusion'. Admitted shortly after, she was pale, restless, ill-looking and mentally confused. A furred tongue and proteinuria were the only abnormal physical signs found.

June 16	Whole blood NaCl	421 mg. %	
June 17	Alkaline treatment stopped		
June 20	Blood urea nitrogen	70 mg. %	
June 20	" "	69 "	
June 30	" "	23 "	
Sept. 12	" "	38 "	Whole blood NaCl 461 mg. %

Clinical recovery was complete in eight days. Two months later she was again placed on alkalis and five days later complained of headache, diarrhoea, thirst, a foul taste in the mouth and weakness of the legs. On leaving off the alkalis she felt quite well in forty-eight hours.

Case 6. Female, aged 58 years. In this case there was a twenty years' history of gastric ulcer. In 1928 alkaline treatment was started with good results, but the following year symptoms of obstruction began to be manifest. For three months before admission, in July 1930, she had been taking large amounts of a powder containing bismuth, calcium, and magnesium carbonate, but no sodium bicarbonate. She was admitted looking extremely ill, with bloodshot eyes, severe epigastric pain, extreme thirst, and a foul taste in the mouth. The urine was strongly alkaline and contained protein. No tetany or other abnormal signs were found on examination.

Blood examinations showed:

July 26	Blood urea nitrogen over 117 mg. %	Blood NaCl 339 mg. %
	Alkaline treatment stopped	
July 28	Blood urea nitrogen 108 mg. %	Blood NaCl 421 mg. %
Aug. 5	Blood urea nitrogen 38 mg. %	

Clinical recovery was complete in three days. Laparotomy subsequently showed an hour-glass contraction of the stomach.

Case 7. Male, aged 46 years. Whilst under observation in hospital as a case of peripheral neuritis, this man had two coffee-ground vomits, which were regarded as being due to a gastric ulcer. Put on the alkaline diet, he showed symptoms of 'alkalosis' in twelve days, viz. malaise and 'pains all over'—the urine contained protein and casts.

Date.	pH.	Plasma CO ₂	Non- protein nitrogen.	Urea nitrogen.	Blood phosphate.	Plasma phosphate.	Bloo NaCl.	Plasma NaCl.
Sept. 19	—	—	—	173	—	—	—	—
	Alkaline treatment stopped							
Sept. 20	7.30	98	120	94	4.5	5.2	434	517
Sept. 27	7.35	71	55	28	2.3	2.9	482	581

Recovery was rapid, being complete in three days. Although the only pH determinations made were normal, the other blood findings were typical of 'alkalosis'. From the urea nitrogen figures recovery had begun before the blood pH was estimated.

Case 8. Male, aged 35 years. For the previous three years he had been on alkalis for a gastric ulcer, with good clinical results. He was admitted to hospital in October 1930 with a recurrence of symptoms and put on intensive alkalis (10 grm. of sodium bicarbonate per diem) and six days later developed headache, backache, general malaise, a foul taste in the mouth, and bloodshot eyes. The urine contained protein and casts. After four days of these symptoms the blood urea was found to be 280 mg. per cent. (= 130 mg. nitrogen), the alkalis were stopped and recovery was complete in forty-eight hours. Three weeks later the blood urea nitrogen was 26 mg. per cent. and the urea concentration test gave a maximum of 1.3 per cent.; three months later the blood urea nitrogen was 25 mg. per cent. and the maximum urea concentration was 2.2 per cent. The urine then contained no protein.

Case 9. Male, aged 46 years. This patient had had a three years' history of intermittent dyspepsia and had been on alkalis for one year. Five weeks before admission he became worse, with vomiting, and six days before admission became extremely ill and drowsy. During this time alkalis had been given freely. On admission he was emaciated, dehydrated, and com-

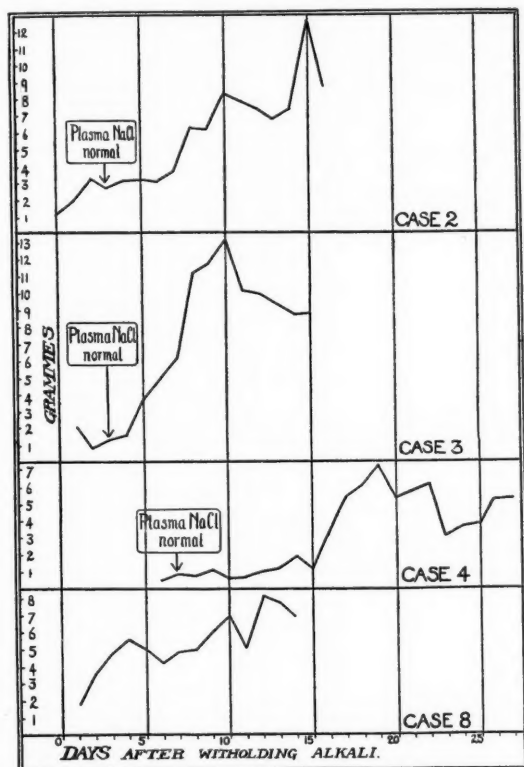


FIG. 3. The daily output of sodium chloride in the urine in four cases.

pletely demented with delusions of persecution. The eyes were bloodshot, but physical examination of the heart, lungs, and nervous system was negative. The urine was alkaline and contained protein.

Date.	Plasma CO ₂	Urea nitrogen.	Blood NaCl.	Plasma NaCl.	Blood phosphate.	
Nov. 16	—	165	225	—	8.2	
Nov. 17	125	180	270	353	10.4	4.9 gm. NaCl intravenously
Nov. 18	94	213	407	504	8.3	7.7 " " "
Nov. 19	73	252	441	546	—	15.3 " " Died "

Post mortem, a large chronic ulcer was found just on the stomach side of the pylorus, with no demonstrable obstruction. The kidneys were large, smooth, and very engorged with blood. The other organs appeared normal.

Sections showed that the ulcer was carcinomatous and that the kidneys were the seat of chronic interstitial changes and of a terminal acute nephritis.

Urine. Daily examination of the urine in five of these cases showed proteinuria and cylindruria which gradually diminished and had cleared up in three or four weeks. The daily output of urea and phosphorus showed no characteristic changes, but only the diurnal variations associated with diet, and, in the case of the former, a rise coincident with the excretion of the excess blood and tissue urea. The chlorides, on the other hand, showed a fairly constant change, namely, very low values during the 'alkalosis' and for some days afterwards, followed by a rise to normal figures. The rise in urinary excretion lagged behind the return to normal of the plasma chlorides by four to eight days (Fig. 3).

Discussion

Why these toxic symptoms should occur in a proportion of patients with peptic ulcer who are otherwise apparently healthy is a question which can be very imperfectly answered. Examination of the blood findings in 'alkalosis' following the alkaline treatment of peptic ulcer shows that they bear a striking similarity to the blood findings in excessive vomiting. For example, three cases of excessive vomiting from pyloric stenosis, occurring during the same period as the 'alkalosis' cases, showed:

	pH.	Plasma CO ₂	Urea nitrogen.	Blood NaCl.	Plasma NaCl.
Case A	7.37	140	65	249	329
Case B	—	115	60	—	324
Case C	7.42	113	133	474	552

In five of my cases vomiting did occur, but it was never severe before the 'alkalosis', and usually appeared as a late manifestation after the patient had been ill for several days with the symptoms. Although it is generally supposed that the systemic effects of alkaline therapy are due chiefly to the soluble alkalis, sodium bicarbonate and citrate, the possible effects of the insoluble alkalis must not be overlooked. By 'fixing' the gastric acidity they prevent neutralization of the alkaline pancreatic juice which is probably re-absorbed from the small intestine. The phosphates and carbonates of calcium and magnesium given by the mouth do not, however, cause the urine to become alkaline. Hardt and Rivers saw alkalosis come on following the addition of calcium carbonate powders to the ordinary alkaline diet, and Case 6 reported in this paper took powders consisting only of the carbonates of bismuth, magnesium, and calcium. The great rise in blood-bicarbonate argues a failure of excretion of the alkali and possibly an impairment of renal function. A normal man can excrete as much as 7 gm. of sodium bicarbonate per hour, which gives an ample margin for the excretion of the ordinary amounts of alkali used, not to mention the other adjustments of acid-base balance—CO₂ retention and lowered ammonia production. In a normal man the intake of 50 gm. of sodium bicarbonate daily makes no difference to the blood constituents except for a slight rise

in the CO_2 combining power of the plasma—up to high normal values. The failure to excrete adequately only some 15 grm. or less of sodium bicarbonate daily points to a disturbance of renal function.

In the cases collected, the urine was mentioned as being abnormal (i.e. containing usually protein and casts, and sometimes blood and pus) in thirty-three cases and normal in four cases; in thirty-one cases there was no reference to the urine. The occurrence of protein, casts and pus in the urine, together with an increase in the urea, creatinine and inorganic phosphorus of the blood naturally suggests some renal lesion, and the questions therefore arise: (a) Is there aggravation of pre-existing renal insufficiency? (b) Are the kidneys damaged by the alkalis? or (c) Can these findings be attributed to extra-renal causes?

(a) Previous renal damage is referred to in general terms as a predisposing cause of alkali intolerance by Hardt and Rivers, Gatewood (1925), and by Hurst, Houghton, Venables, and Lloyd. Venables had one case in which nephrectomy had been done 'for cystic kidney' ten years before, and two cases in which a slight rise in blood urea was present before alkaline treatment began. No previous estimations of blood urea had been made in the other cases, but the persistence of a raised figure after recovery from the alkalotic attack in two cases was thought possibly to indicate previous renal insufficiency. Bloch and Serby, out of sixty cases of ulcer treated on alkalis, noted proteinuria in three before treatment, and Wildman in two cases out of the four which he reported. Hardy's case had had a nephrectomy ten years previously. Of my cases, none had proteinuria before treatment, but two had had scarlet fever in childhood. On the whole there seems to be no convincing evidence of previous renal insufficiency in most of the reported cases, although there is every *a priori* reason to suspect it as a possible aggravating cause.

(b) The effects of alkalis on the kidney have been investigated experimentally by Fischer who injected large amounts of caustic soda solution into rabbits, and found that proteinuria and haematuria followed. No reference is made to the microscopic findings. Kellert found that sodium bicarbonate injected intravenously in rabbits caused transient proteinuria and cylindruria, and Palmer and Henderson made similar observations in man by oral administration. These experiments are of little value in assessing the possible effects of therapeutic alkalis on the kidneys because they consisted of one large dose only. The long-continued administration of alkalis in animals has been carried out by Addis, MacKay, and MacKay, who gave rats 4 grm. of sodium bicarbonate per diem mixed with a normal diet, over periods of nearly a year. The control group of 78 contained 2 cases of haematuria, while the alkalinized group of 72 had 24 cases of marked haematuria, and in addition, 7 of the 24 rats with haematuria had hydronephrosis of one or both kidneys. Microscopy revealed no difference between the kidneys of the two series, but the rats on alkali had blood ureas averaging 36 as against 29 mg. per cent. in the controls. Nuzum, Seegal,

Garland, and Osborne fed animals on *highly artificial diets*, including soya bean, which causes an alkalosis, and found that 'long-continued disturbance of the acid-base balance of rabbits on the alkaline side is capable of causing a moderate hypertension and of causing kidney damage'. Stieglitz considers that 'an alkalosis, as may be produced by long-continued or excessive administration of alkalis, causes distinct renal irritation and occasionally a true nephrosis. Renal injury may result in impairment in the function of neutrality control and thereby affect the tissues as a whole.'

Clinically, the resemblance between the conditions of uncompensated alkalosis and uraemia has been commented on by several authors, and judging from the urea concentration factors of the cases and the urea concentration tests done on Cases 1, 2, 4, and 8, the kidney function during the attack is definitely impaired. It may be argued, on the other hand, that these figures are vitiated by the diuresis which is usually present. My colleague, Dr. W. E. Chiesman, has since examined the blood creatinine and the creatinine filtration rate in two similar cases and found by this method a definite impairment of renal function during the attack.

(c) Wildman and others have attributed a large proportion of the symptoms of uncompensated alkalosis to the hypochloraemia which is almost invariably present, and it may be noted that patients on the alkaline diet have a low salt intake of 2 to 3 gm. daily instead of the normal 10 to 15 gm. Similar symptoms have been found experimentally in dogs with salt deprivation by Frouin and others. The rise in blood urea has been explained as due to increased protein catabolism and as a compensatory mechanism whose function it is to keep up the osmotic pressure of the plasma which is lowered by the hypochloraemia. This theory has been applied with plausibility to the blood findings in excessive vomiting, notably by Hartmann and Smyth, but it is not applicable to the hypochloraemia of alkali excess because the fall in chloride almost exactly balances the rise in bicarbonate. Furthermore, in other conditions with grave chloride loss and the depletion of the blood chlorides, namely, war gas-poisoning and burns, no rise in blood urea has been found (Underhill and Underhill, Carrington, Kapsinow, and Pack).

On the evidence available, the explanation seems to be that in some way alkali excretion is impaired, and the resultant alkalosis lowers renal efficiency. A vicious circle is set up in which increasing alkalosis diminishes renal efficiency and vice versa, and unless alkalis are stopped, death will result. It has been observed that the rise in CO_2 combining power of the plasma precedes the nitrogen rise and, during recovery, the fall in CO_2 combining power precedes the fall in nitrogen. The recovery of renal function is shown by the rapid excretion of the retained urea and phosphorus, by the return of the chloride excretion after the plasma chloride has been normal for some days, and by the disappearance of protein and casts from the urine. In the cases where the urea concentration test was repeated, an improvement in renal function was found over a period of several months. In the

fatal case (No. 9) where alkalis had been pressed for weeks in ignorance of the correct diagnosis, although the blood bicarbonate fell and the chlorides rose to normal in three days, there was a steady rise of blood urea together with progressive oliguria till death resulted from complete renal failure. In the non-fatal cases, it is suggested that there was a disturbance of renal function of such degree that no permanent damage resulted and recovery was possible when the alkali intake was stopped.

Summary

The clinical and chemical features of 'alkalosis' may be summarized as follows—typically the condition occurs in a man aged 35 to 55 years with an ulcerative lesion of the stomach at or near the pylorus, not necessarily with any clinical or X-ray evidence of pyloric obstruction, and not necessarily with any symptoms or signs pointing to impaired renal function. After about a week of intensive alkaline treatment he complains of headache, dizziness, backache, pain and tingling in the limbs, thirst, an unpleasant taste in the mouth, loss of appetite with a particular distaste for milk, abdominal pain, vomiting, drowsiness and occasionally a craving for salt. Physical examination shows that he has slight fever, rapid pulse, slow respiration, and that he looks ill with a shrunken, dehydrated, flushed face, furred tongue, and bloodshot eyes. The urine, strongly alkaline, contains protein and casts, and there is usually a diuresis. No abnormalities can be detected in the heart, lungs, or abdomen, but examination of the nervous and motor systems may reveal some heightened neuro-muscular irritability, more apparent on direct stimulation by tapping the muscles or by the galvanic current than by reflex stimulation. Sensory hyper-irritability is shown by the tenderness of the muscles on pressure, so much so that attempts to take the blood-pressure may be frustrated by the pain which is caused by the sphygmomanometer cuff. At the same time the patient displays mental changes of which the most striking feature again is hyper-irritability. A man usually of a complacent disposition becomes querulous and irritable, grumbling unreasonably about the most trifling annoyances, and may even have delusions of persecution. Chemical examination of the blood gives the following findings:

pH of plasma	7.5	Normal	7.3 to 7.4
CO ₂ c.p.p.	100	"	53 to 78 vols. %
Non-protein nitrogen	120	"	20 to 40 mg. %
Urea nitrogen	100	"	10 to 20 mg. %
Creatinine	5	"	1 to 2 mg. %
Plasma phosphate	6	"	3 to 4 mg. %
Plasma NaCl	490	"	570 to 620 mg. %
Whole blood NaCl	400	"	450 to 500 mg. %

A rise in haemoglobin and a slight rise in serum sodium have also been recorded.

The urine is increased in amount, a diuresis of 2,000 to 3,000 c.c. being not uncommon. A small amount of protein and a few casts, mostly granular and epithelio-granular, are present. The daily excretion of nitrogen, urea, and phosphate is little changed, but chloride and ammonia are almost absent from the urine. In severe cases lactic acid and ketone bodies appear in the urine in pathological amounts.

The simplest chemical procedures available for confirming the clinical diagnosis are blood-urea estimation and the silver-nitrate test for chloride in the urine.

If treatment with alkalis is persisted in, all the changes become more marked, especially the drowsiness; tetany appears, followed by generalized convulsions, collapse, coma—with incontinence of urine and faeces—and death supervenes. If the administration of alkalis is stopped in time, clinical recovery is rapid, the patient being free from symptoms in three or four days. The blood findings return to normal in about ten days, but the excretion of chloride in the urine does not occur in appreciable amounts until a week later. The proteinuria and cylindruria gradually diminish and cease in a few weeks.

Subsequent investigation of the renal function by estimations of blood urea and urea concentration tests show a return to normal in a month or two. A patient who has once had an attack of uncompensated alkalosis always shows himself intolerant of alkalis in the future, and following the attack, remains free from gastric symptoms for some months afterwards without any treatment.

The treatment of 'alkalosis' consists of early diagnosis and the stopping of alkalis. The administration of acidotic drugs does not appear to hasten recovery, and if large doses are used, may actually be dangerous.

It is a pleasure to acknowledge my indebtedness to Professor H. MacLean and to Professor O. L. V. de Wesselow for their interest and advice in connexion with this work.

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MACROCYTIC HAEMOLYTIC ANAEMIA¹

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With Plates 33 and 34

Introduction

DURING the past five years I have seen a considerable number of cases of macrocytic haemolytic anaemia which resembled, in some ways, pernicious anaemia and, in others, familial acholuric jaundice. Careful investigation revealed, however, that they belonged to neither of these diseases, and further, that several entirely different aetiological factors could produce an apparently similar blood picture. Prognosis and treatment being totally different from that of pernicious anaemia, correct diagnosis becomes a matter of great importance. Accordingly, representative cases have been selected from this series and are described in considerable detail. This report must be considered merely as a clinical record of a series of cases. No attempt has been made to review or discuss the literature on haemolytic anaemia.

The cases may be divided into two groups, namely, haemolytic anaemias secondary to known aetiological causes, and others for which no cause could be found during life or *post mortem*. These groups can be subdivided according to the causal or pathological condition present:

Acquired haemolytic anaemia

Group I.—Causal condition known:

- (a) Due to Hodgkin's disease: Cases 1, 2, 3.
- (b) Due to lead poisoning: Case 4.

Group II.—Causal factor unknown:—

- (a) Histology of spleen resembling that found in pernicious anaemia: Cases 5 and 6.
- (b) Histology of spleen resembling that found in acholuric jaundice: Cases 7, 8, and 9.

Description of Cases

Case 1. J. S., female, aged 59. Admitted to Chalmers Hospital, Edinburgh, 13 February 1928, complaining of weakness, tiredness, and shortness of breath.

¹ Received June 2, 1932.

History. The patient stated that for the past year she had been getting more easily tired and had found great difficulty in doing her house-work. She was so 'used up' by August 1927, that she had to give up work and take a holiday. She returned somewhat stronger, but had never felt well since then, although she managed to carry on her house-work. About two weeks before being admitted to hospital she noticed that she was becoming yellowish, and she began to feel weak and breathless on slight exertion. Her ankles were swollen at night. She called in her doctor, who sent her to the above hospital, where she was admitted under the care of Dr. Fergus Hewat.

Previous illnesses. She had had 'gastric ulcer' when a young woman: rheumatic fever ten years previously.

Family history. In spite of careful questioning no evidence of a familial history of anaemia or jaundice was obtained.

State on examination. The patient was a well-developed woman with little loss of subcutaneous fat. Her skin was extremely pale and had a definite icteric tinge, which was also visible in the conjunctivae. The mucous surfaces were also extremely pale and anaemic. For her age she had a remarkably youthful appearance, and no grey hairs were visible.

Alimentary system. There was no history or sign of glossitis. Her teeth, which she stated were extremely bad, had been removed ten years previously. Except for a poor appetite, she complained of no symptoms related to the gastro-intestinal tract, and nothing abnormal could be found on physical examination.

Fractional test meal (14.5.28). Fasting juice—30 c.c. clear, green fluid; charcoal nil; mucus—trace; bile present; blood absent; free HCl (Gunzberg test) absent; lactic acid (Maclean test) absent.

Faeces. The colour was darkish. Bile was present. Blood was absent. No history of the passage of light, clay-coloured stools could be elicited at any time.

The liver was enlarged, the edge being palpable three finger-breadths below the costal margin. It felt smooth and soft and was somewhat tender.

The spleen was palpable two finger breadths below left costal margin. Slightly tender.

The pulse-rate was 120, regular in time and force, weak and of low pressure. *Blood-pressure*: systolic 112; diastolic 58. Arteries not thickened.

The apex-beat was easily palpable in fifth interspace but displaced slightly outward. On auscultation soft haemic murmurs were heard over the base, and, in addition, a presystolic murmur at the mitral area, with reduplication of the second sound, was present. Mitral stenosis was diagnosed. The heart-sounds were weak and a gallop rhythm was present. Oedema of the ankles, which had been present previously, had disappeared.

Nothing of importance was found in the respiratory, nervous, and urinary systems.

Haemopoietic system: there was no enlargement of lymphatic glands.

On February 15, 1928, the blood count was as follows:

R. B. C.	840,000
Reticulocytes	40 per cent.
W. B. C. (including nucleated R. B. C.)	25,800
Haemoglobin	22 per cent.
Colour index	1.4

Stained blood films :

I. *Erythrocytes.* (a) Marked anisocytosis was present. The mean diameters of the cells varied from 4 to 13 μ . (Price-Jones method.) (b) Megalocytosis was a very prominent feature. Large numbers of cells with diameters from 9–13 μ were present. Many of them were markedly polychromatic: ovality in shape was very noticeable. (c) Polychromasia was present in every second or third cell. (d) Vital staining showed that reticulation was present in 40 per cent. of the R. B. C.

II. *Nucleated red cells.* These cells were present in great numbers: as many as six were seen in one microscopic field. The percentage count of all types of nucleated cells, both white and red, was as follows:

Megaloblasts	16.5
Normoblasts	25
Polymorphonuclear leucocytes	35
Lymphocytes	14
Myelocytes	7.5
Myeloblasts	1.5

Since the total 'white count' was 25,800, the number of the nucleated R. B. C. per c.mm. was over 10,000.

Appearance of nucleated R. B. C. Owing to the great numbers of these cells the opportunity was taken of making a detailed study of their appearances when stained by ordinary and vital methods.

It is unnecessary to state here the histological appearances which influenced the classification of the cells into the megaloblastic or normoblastic series, since the standards adopted by leading haematologists were adhered to. It is of interest, however, to recall that vital staining methods have only become routine clinical procedures during the past four or five years, as a result of the publication of Minot and Murphy's original paper on liver therapy. Considerable diversity of opinion existed at that time in regard to the nature and origin of the reticular material. The case described here, with its great numbers of reticulated cells, both nucleated and non-nucleated, provided excellent material for the study of this problem. All the megaloblasts and the majority of the normoblasts showed a well-marked reticulum surrounding the nucleus. No relation was found to exist between the amount of reticulum present and the degree of nuclear degeneration seen. Indeed, megaloblasts with intact nuclei, often showed a denser reticulum than cells containing nuclei in the later stages of karyorrhesis or karyolysis. It was concluded both for these reasons and from other experiments, as published elsewhere (1 and 2), that the reticulum was certainly of cytoplasmic origin.

Blood-platelets. These elements were large in size and were generally lying singly, as is so commonly seen in pernicious anaemia. On the other hand, while no count was made, I am of the opinion that they were more numerous than one would have expected in a case of pernicious anaemia of similar severity.

White cells. February 17, 1928. The differential white count was:

Polymorphs	62 per cent.
Lymphocytes	24 "
Myelocytes	12 "
Myeloblasts	2 "

The relative proportion of polymorphs to lymphocytes was approximately that found in health, but the presence of myelocytes and myeloblasts in the

circulating blood denoted a very severe derangement of the bone-marrow function.

Van den Bergh reaction :

Direct	Negative.
Delayed direct	Weakly positive.
Indirect	Positive.

Denoting haemolytic (non-obstructive) jaundice. Icterus index—16 units.

Fragility tests. Oxalated blood samples from a normal person, a case of pernicious anaemia, and this patient, were washed and tested against hypotonic saline. The result showed that the pernicious-anaemia blood was more resistant, while the patient's blood was less resistant than the normal control to hypotonic saline. Haemolysis began at 0.5 per cent. saline and was complete at 0.35 per cent. The test was repeated a week later and the result confirmed.

On admission the temperature was 99.8°, but by the fourth day (February 17) it was normal. The patient remained in an apyrexial condition till February 28, when the temperature rose to 99.2°, and then in a step-ladder fashion reached 101° on March 5, when it started to fall again, reaching normal on March 8. No further pyrexial attacks occurred until April 21, when a period of fever lasting eight days and reaching 100° was present. The importance of the febrile attacks in the diagnosis will be discussed later, but it is necessary to note here that the earlier ones were accompanied by marked blood changes.

Thus, by February 21, following four days of apyrexia, films showed that the nucleated R. B. C. were greatly reduced in number. A similar finding was observed in the white count. The percentage figures were :

Megaloblasts	6
Normoblasts	3
Polymorphs	57
Lymphocytes	27
Myelocytes	6
Myeloblasts	1

The percentage-reticulocyte count, however, remained as high as ever and was approximately 50 per cent. The red cell count had risen during the week to only 1,000,000—an increase of 160,000 cells.

On March 2 the reticulocyte count was 70 per cent., the blood picture in other respects remaining unchanged.

Up to this point the patient had been treated with liq. arsenicalis by the mouth, but now she was given the equivalent of 500 gm. of liver in the form of an extract which was known to be potent.

On March 8, Professor Gulland, who had previously merely seen one of the original films, was asked to make a blood examination and reported as follows :

‘The white count is now nothing like so high as it was when the case first came into hospital. The differential count is :

Lymphocytes	60 per cent.
Polymorphs	30 ”
Myeloblasts	4 ”
Eosinophils	6 ”

and to each 100 white cells there are 6 megaloblasts and 9 normoblasts.

The colour index is obviously above unity. There is great irregularity in size and shape, practically no granular basophilia is present, but the reticulocytes are extremely numerous and in some parts of the films practically every red cell is of that type. I am beginning to wonder whether she is not really a leukaemia.'

On March 14, Professor Gulland again made an examination and reported as follows :

'A definite improvement in the blood has taken place :

R. B. C.	1,290,000
Hb.	30 per cent.
C. I.	1.2
W. B. C.	7,000

Differential count :

Lymphocytes	56 per cent.
Polymorphs	36 "
Eosinophils and basophils	8 "

and only about four nucleated red cells to 100 white cells are present. Reticulocytes are very nearly as numerous as before. As she stands now she is an ordinary pernicious anaemia.'

On March 24, 1928, the blood count was :

R. B. C.	1,280,000
Hb.	35 per cent.
C. I.	1.4
W. B. C.	4,400
Reticulocytes	50 per cent.

Microscopic examination of stained blood films showed that marked anisocytosis and megalocytosis were present, and little change could be seen in the red blood-cell picture at this date from that found in the early films, except that nucleated red blood corpuscles and myelocytes were more difficult to find. The white cell count had changed from a leucocytosis to a leucopenia with a relative lymphocytosis.

Liver therapy had, at this date, completely failed to produce the dramatic effects which we are accustomed to see in cases of pernicious anaemia. In spite of daily doses, equivalent to 500 grm. of whole liver, for the period of three weeks from March 2 to March 24, an increase of only 280,000 cells per cm. had been produced.

From this date, however, the patient slowly improved, developing a better colour, and her strength gradually increased.

On April 4, 1928, the blood count was as follows :

R. B. C.	2,000,000
W. B. C.	4,200
Hb.	50 per cent.
C. I.	1.25

Very slow progress was made, but the red cell count gradually increased, while the percentage of reticulocytes became less. Blood-platelets, although large in size, were still present in comparatively large numbers. The patient's physical condition coincidentally improved. The haemic systolic murmurs disappeared, but the organic presystolic murmur remained.

On May 16, 1928, the blood count was :

R. B. C.	3,470,000
Hb.	60 per cent.
C. I.	0.9

The patient returned home. Although much improved she did not appear to me to be cured, and as the diagnosis of pernicious anaemia was open to grave objections it was decided to keep in close touch with the patient, in order to re-admit her to hospital for further observation should a relapse occur. She was given full instructions regarding the importance of continuing liver therapy.

At this point it would appear advisable to discuss the diagnosis of the blood condition present. The result of the blood examination made on February 15, 1928, when a severe anaemia of a high colour index was found, was in favour of the diagnosis of pernicious anaemia. This impression was strengthened by my first inspection of the patient. The absence of any loss of subcutaneous fat, the presence of the icteric tinge, the indirect van den Bergh reaction, and the gastric analysis were typical. The appearance of the red blood corpuscles, when stained by ordinary methods, were pathognomonic of pernicious anaemia except for the abnormal degree of polychromasia. On the other hand, her youthful appearance was against the diagnosis, since it has been pointed out by many observers that pernicious anaemia cases show many signs of premature senility, especially grey hairs at an early age (3). Next, I had never seen a case of pernicious anaemia with a leucocytosis of such dimensions, containing so many immature marrow cells, although a moderate degree of dissociation in the Arneth count to the left and to the right is not uncommon. Lastly, and most important, vital staining methods revealed the fact that the blood was flooded with reticulocytes. In no case of pernicious anaemia in the relapse stage previous to treatment have I found more than 5 per cent. of these cells, and in most cases reticulation occurs in 0.5 to 2 per cent. of cells, which are usually megalocytes. A few days after liver treatment has started the percentage reticulocyte count may reach 50 per cent. or more, and the red blood corpuscles subsequently increase by approximately 100,000 per day, while the reticulocytes return to their normal level of 1 per cent. within a fortnight. In this patient, in spite of 50 per cent. of the red blood corpuscles showing reticulation, practically no change in the count occurred during several weeks. The presence of a large number of reticulocytes in the circulating blood is certain evidence of the functional activity of the bone-marrow. If the blood count under these conditions fails to rise promptly it is obvious that blood destruction must be proceeding apace with blood formation. Many careful examinations of vitally stained films in previous cases of pernicious anaemia gave me every confidence in believing that whatever else the case might be it was not pernicious anaemia.

The next question to be settled was whether the case was one of acute myeloblastic leukaemia. Cases have been reported in which the white cell count was less than 10,000 per cm. In one of my cases I made the diagnosis

on a white count of 4,400, 98 per cent. of the cells being myeloblasts. The diagnosis was confirmed *post mortem*. Professor Gulland, in his report on March 8, seriously considered the possibility of the case being one of leukaemia. By March 14, however, the absence of abnormal white cells contra-indicated this diagnosis, and the appearance of the film stained by ordinary methods appeared to be typical of pernicious anaemia, so that he reverted to his original diagnosis.

Vitally stained films still showed that reticulocytes were present in great numbers, and with the idea that the anaemia was the result of excessive blood destruction by the reticulo-endothelial tissues, particularly by the enlarged spleen, the fragility of the erythrocytes was investigated. These tests further confirmed the idea that the case was not pernicious anaemia, since in that disease the cells are usually more resistant to hypotonic saline than normal corpuscles, whereas in this case they were definitely more fragile.

The diagnosis of familial acholuric jaundice appeared to be unsatisfactory in view of the absence of a family history and the presence of a macrocytic instead of the typical microcytic blood picture. French writers, however, claim that there is a form of *acquired* acholuric jaundice associated with a high colour index and with a low or normal degree of fragility. Although at this date I had never personally seen such a condition, the picture in this case, namely, icterus, positive indirect van den Bergh, increased fragility, high reticulocyte count, and high colour index, appeared to fit the description of acquired acholuric jaundice.

Lastly, the presence of an organic murmur suggested that the anaemia might be associated with a subacute bacterial endocarditis, although no evidence, apart from the presence of a murmur with pyrexia, was found to support this hypothesis. This aspect is, however, reviewed in a subsequent case.

Thus it will be seen that, on leaving hospital, the diagnosis was still uncertain, and it was a matter of great importance that the further progress should be carefully watched. Accordingly, when a relapse occurred three months later she was admitted, on August 14, 1928, to Ward 33, Royal Infirmary, Edinburgh, under the charge of Dr. Goodall.

State on examination. The patient was extremely weak and breathless and her appearance was very similar to that seen on February 17, 1928. Her temperature was over 102° and she appeared to be gravely ill. She complained of no pain anywhere. Haemic murmurs were present, as well as the previously recorded presystolic mitral bruit. The spleen had greatly increased in size, reaching the umbilicus and filling most of the left half of the abdominal cavity. No enlargement of the liver could be made out. In addition, several enlarged glands about the size of a walnut were present on both sides of the neck in relation to the external jugular veins.

On August 15, 1928, the blood count was:

R. B. C.	1,250,000
W. B. C.	5,000
Hb	30 per cent.
C. I.	1.2

The differential count showed a lymphocyte increase. An occasional myelocyte, myeloblast, and nucleated red blood corpuscle was found. Vitrally stained films showed that an actively functioning bone-marrow still existed, since reticulation occurred in 30 per cent. of the red blood corpuscles.

The remarkably rapid enlargement of the spleen and cervical glands was certainly not in keeping with pernicious anaemia and the diagnosis appeared to be either lymphadenoma or malignant disease. A cervical gland was dissected out and examined histologically. The pathologist reported that the gland consisted of a mass of cells varying greatly in size, many of them being giant cells. Mitoses were numerous. The majority of the cells were undifferentiated and obviously malignant, but the source of the disease could not be defined. The report concluded with the statement: 'It may be malignant Hodgkin's disease or an extremely anaplastic carcinoma.'

In spite of treatment with liver and liver extract the patient failed to improve. Continuous enlargement of the cervical glands and spleen took place and the myocardium became weaker, with progressive circulatory failure. Death occurred on September 24, 1928.

The post-mortem findings, which are given in detail below, show that the patient died of a malignant type of lymphadenoma. The pyrexial periods previously mentioned, when viewed in the temperature charts over a period of months, are typical of the Pel Ebstein syndrome. It should be noted, however, that in any very severe anaemia, including aplastic anaemia, pernicious anaemia, and in the terminal stage of leukaemia irregular attacks of pyrexia may be present for no obvious reasons.

Post-mortem Report by Dr. W. G. Millar

The body was rather emaciated and very pale, with little evidence of post-mortem lividity. There was marked oedema of the left leg and thigh (due to pressure of enlarged lymphatic glands on the left external iliac vein).

Examination of the viscera showed that the main lesions affected the lymphatic system, spleen, bone-marrow, and liver, the remaining organs showing, for the most part, only secondary effects.

The lymph nodes in the cervical, mediastinal, coeliac, lower abdominal, and inguinal regions showed marked enlargement which was most pronounced in the coeliac region. The nodes were fairly discrete in the outlying areas, more confluent in the upper abdomen. They were moderately soft and elastic in consistence and had a pinkish-grey colour and homogenous appearance on section. There was no obvious fibrosis nor any sign of necrosis. Alimentary lymph tissue did not show any morbid change.

The spleen was very greatly enlarged, weighing 1,500 gm. The enlargement was uniform, the organ retaining its normal shape everywhere except at one place where a large, fairly recent, infarct caused a slight elevation of the surface. On section the cut surface was of a dark-red colour and scattered over it were numerous whitish areas of irregular shape and size, averaging about 4-6 mm. in diameter. These areas were well defined from the remainder of the surface and appeared to be scattered in an entirely haphazard manner.

The bone-marrow of the shaft of the femur was dark-red in colour and compact. No lymphadenomatous changes could be detected by the naked eye.

The liver showed little abnormality to the naked eye. No lymphadenomatous areas could be detected. The Prussian blue reaction was faintly positive.

The rest of the organs showed nothing of particular interest, except that there were one or two minute recent vegetations in the aortic and mitral valves, and a moderately well-marked mitral stenosis, evidently of rheumatic origin.

Histology. The histological picture in the spleen and the affected lymph glands was similar to that found at biopsy. The naked-eye distribution and appearance, taken with these histological characters, made the diagnosis of Hodgkin's disease certain.

The absence of fibrosis, the variable character of the cells, with their aberrant mitoses and hyperchromatic nuclei, and the microscopic evidence of extension of the cellular proliferation beyond the gland capsules, indicated the acuteness and 'malignant' character of the disease.

The portal tracts of the liver and the sinusoids showed a moderate infiltration by similar lymphadenomatous tissue. The liver parenchyma showed a scanty deposit of haemosiderin.

Bone-marrow (shaft of femur). A marked erythroblastic hyperplasia was the dominant feature seen in sections of the bone-marrow. Normoblasts and, to a lesser degree, megaloblasts, were present in large numbers, while moderate numbers of myelocytes and myeloblasts were seen. In one or two small areas clumps of cells closely resembling those described in the spleen and lymph nodes occurred. They were, however, less varied in size owing to the absence of the larger giant cell types. These foci consisted entirely of cells of the endothelial type which had completely replaced all bone-marrow cells in that area. The bone-marrow immediately surrounding these microscopic deposits did not show any appreciable difference in the degree of erythroblastic reaction from that elsewhere in the section: a point of considerable significance.

Discussion. The possible causes of the profound anaemia in this case appear to be three: Firstly, the anaemia might be part and parcel of the cachexia associated with Hodgkin's disease and caused by poisoning or malnutrition of the bone-marrow with consequent deficiency in the production of erythrocytes. This explanation, which is probably the correct one for the chronic progressive secondary anaemia occurring in most cases of Hodgkin's and malignant diseases, is untenable in this case both on the results of autopsy, when the marrow was seen to be in a state of active erythroblastic production, and on the blood examination during life, when the persistent presence of a large percentage of reticulocytes shows conclusively that the marrow was reacting strongly.

Secondly, the presence of Hodgkin's nodules in the bone-marrow might be held to be the cause of the anaemia. Against this explanation must be set the facts that the observed deposits were scanty and there was no evidence that the haemopoietic tissue immediately surrounding the deposits was in any way different from the marrow remote from the infiltrated areas. While it is easy to understand that a massive replacement of bone-marrow by foreign cells might lead to a severe anaemia from actual deficiency of myeloid tissue, it is difficult to conceive of a similar result

from the microscopic deposits present in this case. It is possible, of course, that a massive replacement had occurred in the marrow of bones elsewhere and that the erythroblastic condition of the femur was of the nature of a compensatory process. No evidence of such an infiltration is, however, available. In order to connect the deposits as a primary cause of the anaemia it would be necessary to assume that the foreign cells acted as irritants to the bone-marrow, causing a hyperplasia which resulted in the production of cells of a less stable character which in turn were destroyed at an early stage in the spleen and liver. A vicious circle would then arise, leading to a diffuse activity of the haemopoietic tissues. The fact that increased fragility of the erythrocytes was found to be present is in favour of such an hypothesis.

The third alternative to be considered is that the anaemia is primarily the result of excessive blood destruction from hyperactivity of the reticulo-endothelial cells in the spleen and elsewhere, and that the bone-marrow reaction is secondary and compensatory. For weeks the patient's red cells remained around 1,000,000 cells per cm. of blood, while her reticulocytes averaged 50 per cent. Taking 0.5 per cent. as a normal reticulocyte count of a person with 5,000,000 red cells per cm. of blood, the assumption would be justified that in this case both blood formation and blood destruction were twenty times as great as in health. It is not unreasonable, therefore, to assume that the greatly enlarged spleen (packed with masses of endothelial cells which may possibly have had exceptionally active blood-destroying properties) played the most essential part in the production of the anaemia. Additional evidence in favour of this hypothesis may be found in the subsequent cases reported in this paper, in which identical blood pictures are described in cases which were certainly not lymphadenoma or any disease in which metastatic deposits in the bone-marrow could occur.

Case 2. Male, aged 60. Admitted to the Royal Infirmary, Edinburgh, 12.12.28, complaining of extreme weakness and breathlessness.

History. About twelve months previously the patient noticed a swelling below the angle of the jaw, on the left side of the neck, which on examination was found to be a mass of enlarged cervical glands. A gland was excised and on microscopic examination was found to be lymphadenomatous. The patient remained well for the next nine months, when he began to feel weaker and less fit for his work. He reported to his family doctor, who found the cervical glands considerably enlarged and some evidence of anaemia present. It was decided to treat the glandular enlargement with radium.

While waiting for admission to the Royal Infirmary he became increasingly weaker and more easily tired. A rapidly progressing anaemia developed and an icteric tint of the skin and conjunctivae appeared. His doctor described the rapid downward course of the disease graphically as follows:—
'The patient's symptoms and appearance suggest that he is suffering from a galloping pernicious anaemia.'

State on admission. The patient was a well-developed but definitely emaciated man of middle age. A well-marked icteric tint of the skin and mucous membranes was present. He was extremely anaemic and breathless, and was obviously critically ill. The pulse was rapid and weak. The apex-beat was scarcely palpable. Haemic murmurs were heard at apex and base. Dullness and crepitations were heard at the bases of both lungs. The liver was not enlarged. The spleen was palpable two finger-breadths below the costal margin.

The blood count on 12.12.28 was:

R. B. C.	850,000
Hb.	22 per cent.
C. I.	1.3
Reticulocytes	5 per cent.

In the stained film: marked macrocytosis and anisocytosis present. One megaloblast and three normoblasts found. Cells hyperchromic.

Several enlarged glands could be felt in the left cervical region, beside and below the sternomastoid muscle. They were firm and discrete.

On 13.12.28 the patient was nearly moribund, and in view of the report on the gland excised a year ago it was decided not to give a blood transfusion.

On 14.12.28 the blood count was:

R. B. C.	780,000
Hb.	20 per cent.
C. I.	1.3
Reticulocytes	8 per cent.

The patient died on 15.12.28.

Post mortem. A mild jaundice was present in the subcutaneous tissues everywhere. The mucous membrane of the mouth, oesophagus, larynx, and trachea was deeply bile-stained. There was great enlargement of the glands lying lateral to the left carotid artery. They were situated mainly under the sternomastoid and were found to be considerably larger than expected from external palpation. The largest was the size of a small pigeon's egg. The glands were discrete, firm, and greyish-pink. No areas of caseation or necrosis were present. No lymphadenomatous glands were found on the right side of the neck, in the axillae or mediastinum. The para-aortic chain of glands was enlarged and lymphadenomatous.

The heart was dilated and its walls showed fatty degeneration. No noteworthy changes were found in the gastro-intestinal tract.

The lungs showed bronchitis and oedema present.

The kidneys were markedly anaemic, and showed some cortical tubular degeneration. Prussian blue reaction negative.

The liver was pale and showed fatty changes. The Prussian blue reaction was faintly positive.

The spleen was enlarged to five times normal size. The cut surface was deep red and somewhat soft.

The trabeculae were thickened. The Malpighian bodies were small and inconspicuous. A large number of masses of yellowish-grey material of firm and elastic consistency, varying in size from a pinhead to a pea, were scattered throughout the substance of the organ.

The spongy bony tissue of several ribs was empty and dry, while in others it contained a deep red, erythroblastic marrow.

Examination of the shafts of the humerus and femur revealed about equal amounts of deep red erythroblastic tissue and of fat, some of which showed gelatinous degeneration. The areas of erythroblastic and fatty tissue were sharply defined from each other.

Microscopic Descriptions by Dr. John McMichael

Spleen. There were deposits of Hodgkin's tissue throughout the organ. At the periphery of the nodules there were large clumps of haemosiderin in the endothelial cells. It is noteworthy that the Hodgkin's nodules were virtually avascular, and the phagocytosis of pigment took place at the periphery where the cells of the nodule came in contact with the circulating blood in the splenic pulp. It is impossible to say, however, if the phagocytic cells involved are lymphadenoma cells or merely ordinary splenic pulp cells which have been stimulated to excessive activity by the mass of newly formed tissue.

No Hodgkin's tissue was seen in the liver. Kupffer's cells were laden with iron pigment and often lying free in the sinusoids.

The bone-marrow shows islets of Hodgkin's tissue, and surrounding these in certain areas are zones of marked erythroblastic and leucoblastic reaction.

Case 3. George H., aged 54. Admitted to Aberdeen Royal Infirmary, 25.7.29, complaining of weakness and breathlessness, duration three years.

Family history: his father and mother had died in old age; of four brothers, two were alive and well, one had died of 'paralysis of the legs', the other of an unknown cause.

Previous illnesses. Nothing significant.

Present illness. The patient was perfectly well until three years previously, when he began to feel run down and easily tired. About this time he had pains in his legs, sometimes in one, sometimes in the other. In addition he had some loss of power and felt the sole of his boot dragging along the ground. This disappeared after a month but again returned, and the symptoms had been present at intervals since. During the previous year the weakness had become more general and persistent and he had become paler and had lost weight. Tingling sensation in the legs and sensations of walking on cotton wool had been present recently. In addition paraesthesia of the arms had been noticed. Complained of sore tongue, vomiting after food, and nausea.

Condition on admission. The patient was a poorly nourished, pallid man, with lemon tint of the skin. The tongue was large, pale, and inclined to be dry.

Apart from a pulse-rate of 102 and systolic murmurs at all cardiac areas, nothing of importance was found. The Wassermann reaction was negative.

Alimentary system. Appetite poor. Nausea and vomiting present soon after meals. No haematemesis. Pain was present in the epigastrium shortly after food. Bowels were regular and physical examination of the abdomen as well as rectal examination failed to produce any significant information. The liver was not enlarged. The spleen was not palpable. The benzidine test for occult blood was negative.

Fractional test meal. Free HCl. was present in small amounts.

Radiological examination of the stomach was negative.

Pulmonary and renal systems. Nothing important to note.

Haemopoietic system. Blood count on 27.7.29 :

R. B. C.	1,700,000
Hb.	39 per cent.
C. I.	1.15
W. B. C.	1,250

Differential count :

Polymorphs	56
Lymphocytes	41
Large mononuclears	2.5
Eosinophils	5

One megaloblast noted during the count of 200 leucocytes.

The patient was placed on liver and liver extract and dilute HCl. The blood count on 30.7.29 was :

R. B. C.	1.76 million
Hb.	42 per cent.
C. I.	1.2
W. B. C.	2,800

Differential count same as that on 27.7.29.

Marked anisocytosis, poikilocytosis, and megalocytosis were present, but no nucleated R. B. C. were seen at this examination.

The patient went rapidly downhill, fluid collected in the peritoneal cavity, vomiting and sickness were present, so that the liver diet could not be properly taken, and the patient died on 15.8.29.

Post-mortem Report

Post mortem the diagnosis of lymphadenoma was made on the following grounds :

The spleen was enlarged and weighed 440 grm. The cut surface of the organ showed red prominences which on histological examination were lymphadenomatous nodules. Similar tissue was found in the liver and in the coeliac and iliocaecal glands, the largest of which had a diameter of four centimetres. The glands in the lower left cervical area were slightly enlarged and similarly infiltrated. No enlargement or abnormality was found in the lymphatic glands in any other situation. The bone-marrow in the shaft of the femur was erythroblastic, and the bone-marrow in the ribs was red but fluid.

Discussion. The progressive history of weakness, of anaemia, the central nervous system phenomena, the tongue changes, and the blood picture were all in keeping with the diagnosis of pernicious anaemia. Free hydrochloric acid in the stomach was, however, contradictory evidence, and the post-mortem results reported above clearly show that the case was a macrocytic anaemia secondary to Hodgkin's disease.

Case 4. Mrs. M. G., aged 42. Admitted to the Royal Infirmary, Aberdeen, on March 3, 1931, complaining of abdominal pain, sickness, and vomiting.

Previous history. For many years the patient had had attacks of abdominal pain, lasting a few weeks at a time, with intermittent periods of freedom from symptoms. The pain was epigastric in situation and radiated through to between the shoulder-blades. It had no very definite relationship to food, except that it was made worse by fatty foods. The pain made her sick and the vomit was bile-stained. The appetite was generally good, but she became quickly satisfied on starting a meal. The bowels were constipated. There was no history of epistaxis, haematemesis, melaena, jaundice, or gall-stone colic.

Present illness. About a month previously her doctor reported that she had symptoms of influenza, and at the same time she had severe abdominal pain, much sickness, and vomiting which was bilious. Shortly before admission she became slightly jaundiced and the vomiting continued.

Family history. Nothing of importance.

Examination. Patient was a well-nourished, stoutish woman, with a marked malar flush, through which could be seen an icteric tint. A slight jaundice was visible in both sclerotics. No enlarged glands were palpable on admission or at any time.

No local or general fullness could be seen on inspection of the abdomen, and the only positive sign was a definite area of tenderness in the right hypochondrium over the area of the gall-bladder and liver. Neither the gall-bladder, spleen, kidneys, nor liver could be palpated. The stools were dark brown, oozing orange-coloured fluid suggestive of an increased amount of bile-pigment.

The cardiovascular, respiratory, and nervous systems—normal.

A trace of albumin and sugar was present in the urine. No casts were found. The urine contained no bile-salts or bile-pigments, but Ehrlich's aldehyde test for urobilin was positive.

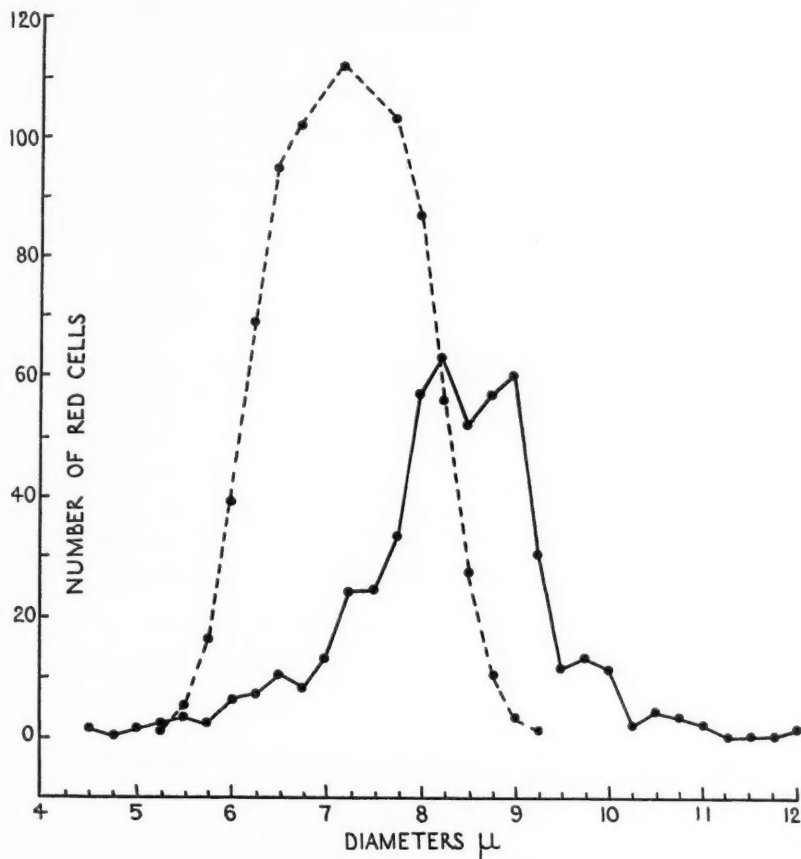
The icterus index of the blood-serum was 33, and the van den Bergh reaction gave a positive indirect and a negative direct action.

The blood count on 5.3.31 was:

R. B. C.	2,500,000
Hb.	55 per cent.
C. I.	1.1
W. B. C. (including nucleated R. B. C.)	7,000
Reticulocytes	5 per cent.

In view of the high colour index and the positive indirect van den Bergh reaction a tentative diagnosis of pernicious anaemia was made. The patient was given 30 gm. of ventriculin daily. On 8.3.31 the blood count was approximately unchanged, but the reticulocyte percentage count had risen to 25. Stained blood films showed a marked macrocytosis which was confirmed by measurement by Dr. Price-Jones, to whom I am indebted (see Graph on p. 557). The mean diameter of the erythrocytes was 8.3 mm. Many nucleated red cells were present, mostly normoblasts, but an occasional megaloblast was found. The differential white count was approximately normal, namely 73.5 per cent. polymorphonuclear leucocytes and 26.5 per cent. non-granular cells, the great majority being lymphocytes. A test

meal was given and a slight degree of hyperchlorhydria was found. The Wassermann reaction was negative. The fragility of the erythrocyte to hypotonic saline was normal. In spite of continued treatment with ventriculin the blood count fell approximately half a million during the next four days.



A rising reticulocyte count and a stationary or falling erythrocyte count are incompatible with a diagnosis of pernicious anaemia. The absence of a family history of anaemia and a normal fragility of the erythrocyte are against the diagnosis of familial acholuric jaundice. Accordingly a diagnosis of acute haemolytic anaemia secondary to a toxic hepatitis of unknown origin was suggested to explain the anaemia, jaundice, vomiting, and pain over the liver. The liver functions were tested by a glucose and a laevulose tolerance test. The blood-sugar curve following the ingestion of 50 grm. of glucose was as follows:

Fasting B.S., 0.09; $\frac{1}{2}$ hour, 0.109; 1 hour, 0.125; $1\frac{1}{2}$ hours, 0.187; 2 hours, 0.162. The fact that the blood-sugar level had failed to return to normal within two hours suggested that some interference with

carbohydrate metabolism was present, and explained the presence of 0.9 per cent. sugar found in the urine.

The laevulose tolerance test showed a rise in the blood-sugar from 0.087 to 0.122 per cent. A rise of 35 mg. per cent. was at least suggestive of liver derangement. The urine was repeatedly examined for crystals of leucin and tyrosin, with negative results. A radiological examination of the chest, abdomen, long bones, and gastro-intestinal tract failed to reveal any abnormality.

11.3.31. The patient was more jaundiced and the urine contained increased amounts of urobilin. Vomiting was severe and intractable, the temperature rose to 101° F., and the mental attitude was confused. The patient had several fits during the next twenty-four hours, consisting of generalized convulsions accompanied by unconsciousness and foaming at the mouth. Bilateral extensor plantar responses were present during the fits, which usually lasted for a few minutes. A flexor response reappeared when consciousness was regained. The symptoms appeared to be in keeping with a diagnosis of cholaemia.

The patient was given glucose by mouth and five units of insulin twice daily.

During the next week the patient's condition improved and, although the blood count remained stationary at 2,300,000, haemoglobin 48 per cent., intense bone-marrow reaction was occurring, since the reticulocyte percentage count had risen from 2 to 25, and many nucleated red cells were seen in the stained blood films.

Improvement continued and by 24.4.31 the count was: red blood-cells 4,300,000; haemoglobin 75 per cent.; reticulocytes 9 per cent. At her own request the patient was sent home and a diagnosis of toxic hepatitis and haemolytic anaemia of unknown origin was the unsatisfactory statement written on her case sheet.

On 19.5.31, less than four weeks later, the patient was sent back to hospital looking extremely ill. Vomiting had returned and she had severe headaches. Pain in the epigastrium was present, for which no cause could be found. A history of convulsive attacks during the previous week was obtained. The blood count had fallen to: red blood-cells 3,000,000; haemoglobin 52 per cent.; C.I. 0.9; reticulocytes 8 per cent. Mental symptoms developed and steadily became more marked. The patient talked to herself and at times became extremely noisy and attempted to get out of bed. Eventually she had to be removed to the Royal Mental Hospital, Aberdeen, under the charge of Dr. Dods Brown. He reported that she was in a state of acute confusion, with complete disorientation for time, place, and person. She had hallucination of sight and was incoherent in her speech. Her physical condition was extremely bad and periodic rises of temperature up to 100° F. occurred. The patient was treated with small quantities of fluid by mouth, two-hourly, the bowel was washed out daily, and rectal salines and glucose were given thrice daily. Later the diet was gradually increased. In about six weeks the confusion passed off, being replaced by a state of depression. She steadily improved and was discharged on October 3, 1931, completely restored to health, both physically and mentally.

On 25.1.32 her family doctor asked that she be readmitted to the Royal Infirmary, Aberdeen. He stated that for some weeks after discharge from the Royal Mental Hospital the patient remained well, but gradually

persistent and intractable epigastric pain and vomiting had returned. During the previous two months the patient had been confined to bed and had steadily got worse.

26.1.32. The patient was readmitted to hospital. She complained of headaches in the left frontal and vertex region, severe constipation, epigastric pain uninfluenced by any factor, bilious vomiting which was not related to food; appetite poor; tongue dirty; thirst marked. Jaundice had appeared and disappeared on several occasions.

Examination again failed to reveal anything to account for the symptoms.

Case 4

Date.	R. B. C.	Hb. %	C. I. %	W. B. C. includ- ing nucleated R. B. C.	Reticulocyte percentage.	Megaloblasts per 100 white cells.	Normo- blasts.	Treatment.
5.3.31	2.5	55	1.1	7,000	5	—	—	Ventriculin 30 grm. daily
Urobilin + + +								
Icterus index 33. Indirect van den Bergh reaction positive. Direct negative.								
8.3.31	2.7	55	1.01	7,000	25	1	10	—
Urobilin +								
10.3.31	2.3	52	1.13	5,000	7	6	8	—
(Price-Jones.)								
12.3.31	2.25	50	1.1	6,000	2	—	—	Glucose 4 oz. daily Insulin 5 units twice daily
Fragility normal. Urobilin + + + Convulsions.								
18.3.31	2.3	48	1.04	9,000	25	1	7	—
Fractional test meal: high normal. Free acid 1 hour 45.								
28.3.31	3.4	80	1.17	6,000	25	—	(Occasional normoblast)	—
12.4.31	3.7	82	1.1	4,800	5	—	—	—
24.4.31	4.3	75	0.8	8,100	9	—	—	—
26.4.31	Discharged							
19.5.31	Readmitted							
"	3.0	52	0.9	—	8	—	—	—
Admitted Royal Mental Hospital. Discharged 3.9.31.								
26.1.32	Readmitted Royal Infirmary							
27.1.32	2.5	45	0.9	—	2	Punctate basophilia prominent		

On 27.1.32 the blood count was:

R. B. C.	2,500,000
Hb.	45 per cent.
C. I.	0.9
Reticulocytes	2 per cent.

Nucleated red blood-cells were absent and polychromatic corpuscles were scanty, while punctate basophilia was marked. The possibility that lead was the unsuspected toxic agent immediately occurred to me, and accordingly the patient was cross-examined regarding the water-supply of her house. At first lead contamination appeared to be ruled out, since the patient stated that she lived in a cottage in the country and that the water for the house was drawn from a well. No water cistern existed in the cottage.

Fortunately cross-examination was continued and the information was elicited that the water was carried by a lead pipe from the well, which was 400 yards distant, and pumped by hand when required. It was obvious that the water would lie for long periods in the pipe, which would act as a lead cistern.

A sample of faeces was submitted to analysis and was found to contain 6.6 parts of lead per 100,000 of faeces. A daily output of 100–150 grm. of faeces would contain approximately 1–1.5 mg. of lead. Two samples of water from the pipe were examined and showed 1.7 and 2.1 parts of lead per 100,000 of water. The maximum content of lead per 100,000 parts of water allowed by the Public Health Authorities is 0.05, so that the water-supply was heavily contaminated. The water-supply of five cottages in the neighbourhood was examined, and all showed excessive quantities of lead. The water in the district was acid in reaction from contact with a peaty soil.

It is interesting to note that no symptoms or signs of lead poisoning were found in the patient's husband, indicating the importance of idiosyncrasy in contracting plumbism.

Discussion. The discovery of the toxic agent made the symptoms which had for so long baffled us perfectly plain. The abdominal pain was a lead colic. It will be remembered that a history of abdominal pain little influenced by food had been present at intervals for many years, but became markedly worse a few months previous to admission to hospital. It is of some interest to note that the lead pipe which had been in use for many years had recently been replaced by a new one. The increased intensity of all the symptoms corresponded in time with this replacement. It is well known that acid water acts much more rapidly on a new pipe than on one coated with a deposit.

The headaches, convulsions, and mental symptoms were due to lead encephalopathy.

The jaundice, pain over the liver, and the alterations (quantitative and qualitative) in the van den Bergh reaction, were the result of a toxic hepatitis. When the absorption of lead is from the alimentary tract and not, as is most common in occupational cases, from the respiratory tract, hepatic lesions would be expected to be particularly intense, as the liver is the first barrier to the poison.

The blood changes presumably were principally due to the toxic effects of the metal on the haemopoietic tissues. The qualitative and quantitative alterations in the serum bilirubin were probably due partly to increased blood destruction and partly to liver damage. The macrocytic hyperchromic blood picture present in this case during the earlier periods of observation is very different from the usual blood changes seen in lead poisoning, namely, a low colour index anaemia together with punctate basophilia. So far as I am aware, no other case of lead poisoning with a similar blood picture has been described. It is difficult to know how a correct diagnosis could have been made during the earlier periods of observation, since the characteristic features of peripheral neuritis were absent, no blue line was present on the

gums, the patient being edentulous, and the blood picture was in no way characteristic.

Case 5. Female, aged 55. On May 20, 1930, I was asked to see in consultation a patient who, her doctor stated, had become progressively more and more anaemic during the past few months.

The patient presented the typical lemon-yellow colour characteristic of pernicious anaemia. Her skin was pale and her mucous membranes were markedly anaemic. Her subcutaneous fat was plentiful and no evidence of cachexia was present. My first impression was that she was undoubtedly a typical case of pernicious anaemia.

History. The patient stated that for the past six months she had become progressively weaker and more easily tired, but she complained of no pain at any time. During the preceding few weeks loss of appetite and vague gastro-intestinal disturbances had been present. The tongue was clean, smooth, and glossy; no history of pain was obtained. Examination of the heart merely revealed haemic murmurs and a tachycardia of over 100 beats a minute. Nothing abnormal was found in the respiratory or gastro-intestinal systems. On palpating the abdomen a large spleen was felt, projecting towards the umbilicus in the line of the tenth rib. No enlarged glands were found in any situation.

The blood count on 20.5.30 was:

R. B. C.	1.5 million
Hb.	35 per cent.
C. I.	1.16
W. B. C.	3,500
Reticulocytes	1 per cent.

A diagnosis of pernicious anaemia was made, and the patient was placed on ventriculin, 30 grm. daily. In spite of this treatment the blood count fell to 1,350,000 red cells on 21.5.30, and to 1,150,000 on 22.5.30. The patient's clinical condition was decidedly worse. Accordingly she was transferred to a nursing home, where she was transfused with one pint of citrated blood. Liver extract, two tubes daily, and small quantities of raw liver were given in addition to the ventriculin, because I believed that I was dealing with a severe case of pernicious anaemia with a considerable degree of bone-marrow aplasia. By 26.5.30 the count had risen nearly half a million—to 1,600,000 red cells, haemoglobin 36 per cent., but the white cell count still remained low, and the reticulocyte count which, on 22.5.30, had advanced to 6 per cent., had fallen again to 2 per cent.

The patient's clinical condition was now very serious, and despite ventriculin, liver, and liver extract, the red cell count steadily fell, till on 9.6.30 it reached 900,000 per c.mm. of blood. Although the erythrocyte count was falling the reticulocyte count was steadily rising, reaching 12 per cent. on 9.6.30. It was obvious, therefore, that the patient was suffering from an acute haemolytic anaemia of unknown origin, and the diagnosis of pernicious anaemia was accordingly discarded.

The similarity of symptoms and signs in this case to Case 1 of this series suggested to me that perhaps the excessive haemolysis was the result of hyperactivity of the spleen, which was possibly the site of Hodgkin's disease. Splenectomy was accordingly advised.

The operation was successfully performed by Professor Wilkie on 10.6.30, the patient being transfused with one pint of citrated blood at the end of

the operation. The spleen weighed 1,700 grm. A marked clinical improvement occurred during the next three or four days.

On 12.6.30 the reticulocyte count was 40 per cent., while the red cells had risen to 1.6 million and the haemoglobin to 35 per cent. By 16.6.30 the red cell count had reached 1.9 million and the haemoglobin 50 per cent. During this period great numbers of nucleated red cells appeared in the peripheral blood, as many as 4,000 per c.mm. being present at one examination. The majority of these cells were normoblasts, but many megaloblasts were also found. The rate of improvement following splenectomy had exceeded our most sanguine expectations, and it was hoped that the removal of the main haemolytic organ would allow the blood-level to rise steadily to normal. Unfortunately this was not to be the case; in spite of continued treatment with ventriculin, liver, and liver extract, the red cell count began to fall. During the period between 18.6.30 and 26.6.30 the count fell by approximately 800,000 cells, while the haemoglobin fell from 50 to 33 per cent. Concomitantly with this fall the reticulocyte count, which on 18.6.30 was 2 per cent., began to rise, reaching 12 per cent. on 25.6.30 and 25 per cent. on 26.6.30, and remained during the next week in the neighbourhood of 20 per cent. During this period the patient's clinical condition became very serious, for not only was she suffering from severe anaemia, but a train of curious mental symptoms started, which made the nursing and feeding of the patient extremely difficult. She suffered from hallucinations and delusions, and for a period of several days failed to recognize either her doctors or her nurses. Following the increased reticulocyte count during the period 25.6.30-3.7.30, the blood count started to rise again, so that by 3.7.30 it had reached 2,000,000 red cells, haemoglobin 60 per cent., with a concomitant increase in the well-being of the patient. By 14.7.30 the reticulocyte count had fallen to 3 per cent. and remained in the neighbourhood of 2 per cent. for a period of many weeks.

On 11.8.30 the patient was removed to a convalescent home, as progress in the nursing home appeared to be stationary. She was able to lie in bed in the garden in the fresh air and sunshine, and was given a well-balanced diet, rich in vitamins, by the addition of radiostoleum and orange-juice. She felt better in the convalescent home, although still very weak, and her appetite improved.

On 8.9.30 the patient's blood count was 3,000,000 red cells, haemoglobin 78 per cent., which was the highest reached. She returned home and, owing to the high haemoglobin percentage, was able to get about and do her household duties.

On 25.9.30 the blood count was 2,500,000 red cells, haemoglobin 70 per cent., and during the next two or three months counts were made on several occasions which revealed the fact that despite large amounts of liver, liver extract, and ventriculin, the red cell level could not be raised beyond the 3,000,000 mark. She returned to light duties in her business, which was a stationer's shop, and continued at this occupation until March, 1931, when it was found that she was again getting progressively weaker.

On 6.4.31 her blood count was:

R. B. C.	1,170,000
Hb.	26 per cent.
C. I.	1.13
Reticulocytes	1 per cent.
W. B. C.	3,100
Lymphocytes	83 per cent.

Case 5

Date.	R. B. C. in millions.	Hb. %	C. I. %	W. B. C. including nucleated R. B. C.	Reticulocyte percentage.	Treatment.
20.5.30	1.5	35	1.16	3,500	1	Ventriculin 3 tubes daily
21.5.30	1.35	30	1.1	2,000	2	" " "
22.5.30	1.15	26	1.13	2,000	6	" " "
25.5.30	Patient transferred to Nursing Home.				Transfusion 1 pint citrated blood.	
	1.4	32	1.14	2,000	5	Liver extract 2 tubes daily and liver
26.5.30	1.6	36	1.12	2,000	3	
30.5.30	1.4	32	1.14	2,000	2	
4.6.30	1.15	25	1.08	2,000	3	
7.6.30	1.0	22	1.1	2,000	8	
9.6.30	0.9	22	1.2	3,680	12	
10.6.30	Operation. Spleen removed, weight 1,700 gm.				One pint citrated blood transfused	
11.6.30	1.5	33	1.1	9,000	20	Liver extract 1 tube
12.6.30	1.6	35	1.09	10,000	40	Ventriculin 10 gm.
13.6.30	1.9	41	1.07	8,000	30	
16.6.30	1.9	50	1.31	7,000	2	
18.6.30	1.95	50	1.28	9,000	2	
20.6.30	1.6	48	1.5	—	—	
25.6.30	1.5	36	1.2	12,000	12	Ventriculin 20 gm. + liver and liver extract
26.6.30	1.2	33	1.37	19,000	25	
30.6.30	1.6	48	1.5	15,000	15	
3.7.30	2.0	60	1.5	8,000	20	
7.7.30	1.87	55	1.48	10,000	7	
14.7.30	2.27	56	1.24	15,000	3	
8.10.30	3.0	78	1.3	—	—	1 tube liver extract or 10 gm. ventriculin + liver daily

Patient remained well and returned to work till March 1931, when she began to get breathless and weak.

6.4.31	1.17	26	1.3	3,100	1	Liver extract (Armour's) 1 oz. daily. Ventriculin 30 gm. daily
15.4.31	0.7	18	1.2	2,300	0.5	
17.4.31	Blood transfusion. Improved for two or three days					
24.4.31	Died.					

Miss T.

W. B. C. including nucleated R. B. C.

Date.	Total count.	Megaloblasts.	Normoblasts.	Poly- morphs.	Lympho- cytes.	Mono- cytes.
22.5.30	2,000	(Occasional megaloblast or normoblast seen)		35	47	18
Differential counts done on five occasions between May 20 and June 9 with similar results						
10.6.30	Splenectomy + transfusion					
12.6.30	10,000	3	36	43	12	6
16.6.30	7,000	(scanty)	(scanty)	46	40	14
18.6.30	9,000	”	”	46	40	14
26.6.30	19,000	3	13	35	22	27
30.6.30	15,000	1	7	45	30	17
7.7.30	10,000	(No megaloblasts, occasional normoblast)		40	45	15
14.7.30	15,000	—	1	28	48	23
6.4.31	3,100	—	—	14	83	3
15.4.31	2,300	—	—	10	87	3

Long-continued hyperactivity had evidently resulted in bone-marrow exhaustion.

By 15.4.31 the blood count had fallen to 700,000 red cells per c.mm., haemoglobin 18 per cent., C.I. 1.3. The patient complained of blurring of vision of the right eye, which on ophthalmoscopic examination showed large recent haemorrhages into the retina. On 17.4.31 she was transfused with one pint of citrated blood. Clinical improvement was apparent for two or three days after the transfusion, but on 23.4.31 she was obviously dying, the haemoglobin having fallen to 12 per cent., and she expired on 24.4.31. No post-mortem examination was carried out.

Further haematological investigations. During the first month she was under observation the following investigations were carried out in addition to the red and white cell counts, differential and reticulocyte counts already enumerated:

A test meal was given, and 20 units (Ewald scale) free hydrochloric acid was present in the one-hour sample. Fragility tests were carried out on two occasions, and the fragility of the patient's cells was found to correspond exactly with the control.

Van den Bergh reaction: Immediate direct—negative.
Indirect—positive.
Icteric index—20.

Blood-platelet counts were made on several occasions. Before operation the count was 250,000; after operation it ran between 500,000 and 1,000,000. The blood-platelets were large and usually single. Arneth counts of the white cells were made on several occasions, and in every case a marked shift to the left was found, and never any signs of a shift to the right, which is typical of pernicious anaemia.

The report on the Wassermann reaction on the first specimen of blood was that the serum was anti-complementary. The second specimen, which was taken a fortnight later, was reported to be positive, and in consequence antisyphilitic treatment in the form of iodides and mercury was instituted, and later small amounts of novarsenobillon were given. In view of a similar serological report in three other cases of acute haemolytic anaemia in which the most careful investigation into the history, clinical state, and pathological examination of the organs *post mortem*, and of the spleen removed at operation, failed to show any evidence of syphilis, I am of opinion that the report was probably a false positive, depending on some unexplained factor in the blood.

Price-Jones curves were plotted, and the results found corresponded to the macrocytic appearance of the cells. Although there was a marked shift to the right in the peak there was not the same degree of broadening of the base as is usually found in a case of pernicious anaemia of similar severity. In short, the impression was confirmed that a marked macrocytic anaemia was present, but the coefficient of anisocytosis, i.e. the degree of variability, was only moderate. In addition, the cells were large and round, and not oval as is so typical of the genuine megalocyte of pernicious anaemia.

Report on Liver and Spleen of Case 5 by Dr. John McMichael

The spleen was large, red, and cellular, with no evidence of increased connective tissue. Histologically the essential features were: (1) Proliferation of large, pale cells of the histiocyte type, i.e. undifferentiated spleen pulp

The patient was placed on liver and liver extract by mouth, but no response was obtained. Blood counts done on ten separate occasions between 13/9/28 and 22/10/28 showed a steady fall in the red cell count, until on the latter date it had reached 650,000. The white count remained within the normal limits—6,000 to 10,000; colour index was constantly unity or over, and the reticulocyte percentage count varied from 15 to 60 per cent. Nucleated red cells, both normoblasts and megaloblasts, were found.

Fragility to hypotonic saline. Normal.

Van den Bergh reaction. Delayed direct reaction positive. Indirect reaction markedly positive. A high icterus index was obviously present, as judged by the yellow colour of the serum.

During this period the patient had a temperature which varied from 97° to just over 100°. Her clinical condition was steadily deteriorating, her pulse-rate being in the neighbourhood of 110 to 120.

Blood-pressure. Systolic 98, diastolic 40.

Tests for renal efficiency. Blood urea 32 mg. per cent. Specific gravity remained constantly round 1,010, while albumin was present in considerable quantities all the time. Red blood corpuscles and casts were found on every examination. The systolic murmurs heard at all areas became more marked, and in addition the quality of the murmur at the aortic area appeared to be rougher. The spleen could not be palpated but appeared to be enlarged on percussion.

In view of the complete failure of the patient to react to liver, liver extract, iron, and arsenic, and in view of the fact that marked blood destruction was taking place, as suggested by the high reticulocyte counts with stationary or falling red cell counts, it was decided that the operation of splenectomy should be performed. On 9/11/28 Professor Wilkie removed the spleen. At the same time the patient received 22 ounces of citrated blood. Twenty-four hours after operation the red cell count had risen to 2,000,000 while the reticulocyte percentage count was 30. On the following day the patient became more anaemic again and on 14/11/28 the erythrocyte count had fallen to 1,120,000, reticulocyte count 13 per cent. The white cell count rose to 74,000, 95 per cent. being polymorphonuclear leucocytes, and the Arneth count showed a marked shift to the left. It was obvious that sepsis had taken place. The patient died the following day.

Summary of Post-mortem Examination

Marked oedema of the subcutaneous tissues was present everywhere. Free fluid was present in excess in all the serous cavities.

Heart. Cavities dilated. Myocardium showed marked fatty changes. A small perforating vegetation was present on the auricular surface of one of the cusps of the mitral valve. The pathologist was satisfied that this was of recent occurrence.

Abdominal cavity. Greenish-yellow pus was present, underlying the lower end of the operation wound. The liver was large and showed fatty changes and chronic venous congestion. Prussian blue reaction moderate.

Kidneys. Large and exceedingly pale. Capsules stripped easily, the sub-capsular surface being smooth.

Bone-marrow (shaft of femur) showed a marked erythroblastic reaction.

Spleen. Enlarged (680 grm.), soft in consistence, and dark red in colour.

Microscopic Examination of the Spleen. Report by Dr. John McMichael

The spleen is very cellular with no increase of connective tissue. The arteries show hyalinization of their walls (which is common in the normal spleen). The Malpighian bodies are unchanged and there is no evidence of any increase of lymphoid tissue.

The cells of the spleen pulp are markedly altered from the normal. Instead of the usual reticulo-endothelial cells with clear open nuclei, the majority of the cells have denser nuclei with more abundant cytoplasm. Here and there, especially in the sinuses, primitive blood-cells are seen—nucleated red corpuscles and myelocytes being identified. The whole picture suggests diffuse myeloid metaplasia with a predominance of primitive cell types.

The picture is totally different from that found in ordinary types of splenic anaemia and haemolytic jaundice. This type of reaction is only found in very profound dyscrasia of the haemopoietic system.

Discussion on Cases 5 and 6

The cause of the intense haemolysis which occurred in these two cases is unknown. The haemolytic phenomena present distinguish them from pernicious anaemia, while the histology of the spleen as certainly rules out the diagnosis of familial acholuric jaundice. At one period the diagnosis of ulcerative endocarditis was seriously considered as the aetiological factor in Case 6. The systolic cardiac murmurs altered in quality and became louder and rougher. Blood culture, however, was negative, and *post mortem* the pathologist was satisfied that the small vegetations present on the valves were recent in origin and were terminal phenomena.

Case 7. James McK., aged 19. Farm servant. Admitted to the wards under the charge of Dr. Croll in the Aberdeen Royal Infirmary on September 22, 1931, complaining of weakness, lassitude, and headaches.

History of present illness. Six days previous to admission to hospital the patient had been in perfect health. While at work in the fields on September 14, 1931, he began to suffer from headaches and a tired feeling came over him. The lassitude increased and he was forced to go to bed. During the next three days attacks of sickness and vomiting started.

Previous and family history. The patient's previous health had always been satisfactory. He had never suffered from any serious illness nor had he even been anaemic or jaundiced. A careful inquiry into the family history by his doctor failed to reveal any evidence that his present condition was familial. Living in a sparsely populated country district, in which his family had long been settled, it is almost certain that no member of his family had suffered from anaemia or jaundice.

State on admission. The patient was intensely anaemic, with a well-marked icteric tint of the skin and conjunctivae. Temperature 100. Pulse 132, regular, bounding in character. Blood-pressure 110/50. Apex-beat within nipple-line in fifth interspace. Systolic murmurs at all areas. Liver normal in size. Spleen enlarged to costal margin and just palpable.

Alimentary, respiratory, and nervous systems satisfactory.

Urine. Bile absent, urobilin present.

Haemopoietic system. Blood count on 23.9.31 :

R. B. C.	800,000
Hb.	6 per cent.
Reticulocytes	60 per cent.
W. B. C. (including nucleated R. B. C.)	24,000

The haemoglobin was so low that the blood pipette had to be filled three times and the final calculation divided by three before a reading could be made. Eighty-five per cent. of the white cells were polymorphonuclear leucocytes. A marked shift to the left in the Arneth count was present. An intense bone-marrow reaction was proceeding, as evidenced by the large numbers of reticulocytes and nucleated red cells in the circulation. For every 100 white cells there were 80 nucleated red cells. The great majority were mature normoblasts with nuclei in various stages of disintegration. About 10 per cent. could be described as macronormoblasts and 3 per cent. were sufficiently primitive to be placed in the category of megaloblasts. Intense anisocytosis and polychromasia were seen in the films stained by Giemsa.

Van den Bergh reaction. Immediate direct reaction negative. Indirect reaction positive.

Icteric index 100.

Fragility to hypotonic saline increased. Haemolysis started at 0.6 per cent. saline and was complete at 0.35.

A diagnosis of acute haemolytic anaemia was made, and in view of the exceedingly severe degree of anaemia present it was decided to give a blood transfusion as soon as a suitable donor could be obtained.

On September 24, 1931, one pint of citrated blood was run slowly into a vein, the patient's father being the donor. The temperature rose some hours later to 104° F. and the patient had mild rigors, but by the next day it had returned to 101° F. and within forty-eight hours to normal.

On September 25, 1931, the blood picture was practically identical with that seen on September 23, 1931, except that the number of nucleated red cells in the peripheral blood was even greater. For every 100 white cells 128 nucleated red cells were counted. The total white cell count, including nucleated red blood corpuscles, was 30,000, so that a 'blast' crisis of approximately 17,000 nucleated red blood-cells per c.c. of blood was present.

A rapid improvement in the clinical state of the patient occurred as a result of the transfusion. In five days the blood count had more than doubled, reaching on September 30, 1931: red blood-cells 1,800,000, haemoglobin 25 per cent.

By October 4, 1931, the excessive activity of the bone-marrow was lessening, as judged by the diminution in number of the nucleated red blood-cells in the peripheral circulation, and by the fall in the reticulocyte percentage count to 20. Concomitantly blood destruction had lessened, as noted by a rise in the red cell count to 2,800,000, haemoglobin 40 per cent.

On October 13, 1931, the red cell count was 3,000,000, haemoglobin 52 per cent., and on October 19, 1931, 3,500,000, haemoglobin 61 per cent.

On October 28, 1931, the red cells numbered 4,500,000, haemoglobin 78 per cent., and the patient returned home feeling perfectly well.

On December 4, 1931, the patient was readmitted to hospital suffering from intense anaemia and definite jaundice. His history on this occasion was exactly similar to that recorded in the first haemolytic crisis. The patient had been feeling in good health and doing his farm work regularly, when suddenly, about a week before admission, he began to lose his appetite and feel weak and tired. Headaches, sickness, and vomiting began, so that he was forced to go to bed, and lay completely prostrated.

Physical examination. Skin and conjunctivae extremely pale and definitely icteric. Liver not palpable. Splenic dullness percussible to costal margin, edge palpable. Systolic murmur at all areas. Blood-pressure 126/60. Large quantities of urobilin in urine.

Blood count on 5.12.31 was:

R. B. C.	1,500,000
Hb.	22 per cent.
C. I.	0.73
W. B. C.	10,000
Reticulocytes	40 per cent.

Two normoblasts in a count of 200 white blood-cells were found. The differential white count showed 82 per cent. polymorphonuclear leucocytes, with a marked shift to the left in the Arneth count. A film showed marked anisocytosis and intense polychromasia.

The patient was given 30 grains of iron and ammonium citrate three times a day, but the count steadily fell until on December 11, 1931, it reached:

R. B. C.	750,000
Hb.	10 per cent.
Reticulocytes	50 „

On December 12, 1931, the patient was transfused with one pint of citrated blood. A severe rigor occurred and the temperature, which previously had been swinging irregularly between 98—101° F., shot up to 104° F., returning to 101° F., in twenty-four hours and reaching normal within three days. The result of the transfusion was very disappointing, as the red cell count, on December 15, 1931, was only 850,000, haemoglobin 12 per cent., reticulocytes 40 per cent. Differential count: 82 per cent. granular cells and 18 per cent. non-granular cells (lymphocytes and monocytes). Four megaloblasts and 10 normoblasts to every 100 leucocytes were counted.

A reticulocyte percentage count of 40, with a stationary blood level, was clear evidence that intense haemolysis was still proceeding and that the blood transfusion had failed to stop the haemolytic crisis. It was decided to remove the spleen as soon as the patient's clinical state was suitable. The blood count slowly rose, reaching, on December 30, 1931: R. B. C. 1,730,000, haemoglobin 37 per cent., and on January 5, 1932: R. B. C. 2,300,000, haemoglobin 42 per cent. The differential white count was: 80 per cent. polymorphs, 20 per cent. non-granular white cells.

The patient was transferred to the charge of Sir John Marnoch and the spleen was successfully removed. Thereafter the patient made an uninterrupted recovery. On February 10, 1932, the blood count was: R. B. C. 4,250,000, haemoglobin 75 per cent. and the blood film appeared normal. A fragility test made on the same date showed that no change in the fragility to hypotonic saline had resulted from splenectomy, since haemolysis

began at 0.6 per cent. saline. The patient left hospital looking and feeling perfectly well.

22/4/32. The patient's doctor reports that he has started work on the farm again.

Microscopic Appearances of the Spleen. Report by Dr. John McMichael

The spleen was enlarged to four or five times the normal size. In colour it was very dark red and the Prussian blue reaction was faintly but definitely positive.

Microscopically no abnormality was detected in the blood-vessels or Malpighian bodies. The pulp, however, was intensely congested, red blood corpuscles forming a larger proportion of the field than the spleen elements proper. In spite of this intense congestion there was no marked dilatation of sinuses.

The appearances are characteristic of acholuric jaundice.

Case 8. Female, aged 45. Complaining of general debility and breathlessness.

Previous history. Satisfactory. No history of anaemia or jaundice before the present illness. Nothing of importance in the family history.

Present illness. The patient had been in China for the past ten years, but returned to Scotland in the autumn of 1929. She had been getting more easily tired for some months, and when first seen was exceedingly weak and breathless on exertion.

State on examination. Nutrition fair. An icteric tint of skin and mucous membranes was present. Apart from tachycardia and haemic murmurs, systolic in time, at all areas, nothing of importance was noted. The liver was felt three finger-breadths below the costal margin: its edge was smooth and slightly tender. The lower border of the spleen reached the level of the umbilicus. Its right border reached to the mid-abdominal line. It moved freely with respiration and was slightly tender.

Haemopoietic system. The blood count on 26/2/30 was:

R. B. C.	1,100,000
Hb.	26 per cent.
C. I.	1.4
W. B. C. (including nucleated R. B. C.)	7,000

Differential count:

Polymorphs	43 per cent.
Eosinophils	3 "
Lymphocytes (including monocytes)	41 "
Nucleated R.B.C.	13 "

In the film there was marked anisocytosis and poikilocytosis with intense polychromasia, every second or third cell showing basophilia. Great numbers of nucleated red cells were seen, the majority being normoblasts, but some were sufficiently primitive to be classified as megaloblasts.

Van den Bergh reaction. Immediate direct negative.
Indirect positive.
Icterus index 50.

Urine. Bile absent. Urobilin present in large amounts.

Fragility of the erythrocyte, normal.

Test meal. Free hydrochloric acid present in all fractions.

Wassermann reaction. First test \pm .

Second test -.

The patient was placed on liver and liver extract, but for weeks the blood count showed little change. The reticulocyte percentage count varied from 30 to 50 on different occasions. Eventually the patient was placed on ventriculin and the blood picture slowly improved.

On 3/6/30 the blood count was:

R. B. C.	3,200,000
Hb.	80 per cent.
C. I.	1.3
W. B. C.	9,600

The differential count was similar to that made on 26/2/30, except that 25 per cent. of eosinophil leucocytes were present. Polychromasia was still a prominent feature.

In view of the large numbers of eosinophils present a most careful search was made on several occasions for intestinal parasites. Nothing was found in the urine or faeces to account for the eosinophilia.

On 25/6/30 further improvement had occurred, the red cell count being 3,700,000, haemoglobin 75 per cent. In spite of intensive treatment with ventriculin and liver the blood count started to fall, reaching, on 3/10/30:

R. B. C.	2,500,000
Hb.	70 per cent.
C. I.	1.4

The white cell picture, including the intense eosinophilia, still remained. Polychromasia was marked and nucleated red cells were fairly numerous.

Several remissions and relapses occurred during the next few months. During a relapse the spleen enlarged, jaundice increased, the reticulocyte percentage count rose, and nucleated red cells, including megaloblasts, appeared in the circulation. For the past year a satisfactory blood level has been maintained, in spite of two serious illnesses, viz., several weeks in bed with a pleurisy and more recently a large suppurating cyst removed from the back.

On 15/4/32 the patient's colour was excellent. No signs of jaundice or anaemia were present. She stated that she was feeling extremely well. The liver was four finger-breadths below costal margin; smooth and not tender. There were no ascites or enlarged veins. The spleen was four finger-breadths below costal margin. Its right border was two inches from the umbilicus. It was not tender and moved easily with respiration.

The blood count was:

R. B. C.	5,000,000
Hb.	85 per cent.
Reticulocytes	1 „
W. B. C.	6,600

Case 9. Male, aged 60. Labourer. Admitted Royal Infirmary, Aberdeen, on February 2, 1932, complaining of breathlessness and weakness.

History. Two years previously the patient began to find difficulty in cycling uphill. He suffered also from coldness of the hands and could

scarcely walk for 'rheumatics'. The weakness became progressively more marked, until he had to stop work. He was admitted to the Royal Northern Infirmary, Inverness, in October 1931. The patient had steadily got worse, although there were temporary periods of slight improvement. He first noticed that his skin was becoming yellow in August 1931. Since then icterus had been constantly present, although it had varied in intensity at different times. He became much more yellow two weeks before admission to the Aberdeen Royal Infirmary.

Previous history. Until two years previously the patient had always been a healthy man and had never had any serious illnesses. His family history, which was easily obtained, since he lived in a sparsely populated district, was negative in regard to anaemia or jaundice.

On October 29, 1931, I received a vitally stained blood film from Dr. Bannerman, pathologist to the Royal Infirmary, Inverness, and a letter from which the following extracts are taken: Dr. Bannerman reported that a patient in the Royal Infirmary, Inverness, presented a blood picture of a haemolytic type, and also that the blood possessed to a high degree the characteristic features of autohaemagglutination. On withdrawing the blood into citrate or oxalate solution, it clotted immediately with marked retraction of the clot. It was impossible, he stated, to do an accurate blood count, since clumping occurred in the red cell diluting fluid in the haemocytometer pipette, no matter how rapidly the manipulation was effected. The red cells numbered approximately 1,096,000, haemoglobin 28 per cent., colour index 1.3, white blood-cells 5,680, reticulocytes 50 per cent. Four normoblasts and 2 megaloblasts were counted in every 100 white cells. The patient had a lemon-yellow colour. The test meal showed normal amounts of free hydrochloric acid.

An examination of the stained blood film sent by Dr. Bannerman confirmed the observations quoted above, and in answer to his inquiry regarding the nature of the anaemia I suggested that the patient was suffering from a severe acquired haemolytic anaemia of unknown origin.

In January 1932, when in Inverness, I was able to see the patient, through the courtesy of Dr. Reid, physician in charge of the ward in which he was being treated. The patient was a stout, well-nourished man, with marked lemon-yellow colour, and was suffering from intense anaemia. His appearance was identical with that seen in a severe case of pernicious anaemia. His liver was slightly enlarged and his spleen was palpable. In spite of treatment with liver, liver extract, and ventriculin, apart from slight temporary improvements from time to time, his blood picture and blood count had remained unchanged. The man was critically ill, since the heart-muscle was seriously weakened by the long-continued and intense anaemia. The possible dangers of transfusion in a person with such marked auto-agglutination phenomena, and the operative risk of splenectomy in view of the physical condition, were recognized to be very serious, but having regard to the failure of all previous treatment to arrest the haemolytic process, and to the fact that the patient would certainly die if nothing further was done, I suggested that these measures should be undertaken. Through the courtesy of Dr. Reid the patient was transferred to my wards in the Royal Infirmary, Aberdeen, on February 2, 1932.

State on admission. The patient had travelled 100 miles in an ambulance and was exceedingly weak and ill on admission. The pulse-rate was 132. Respiration 36. Breathlessness marked. Blood-pressure 118/70. Pulse

rapid, regular, and of small volume. Arterial wall (radial, brachial, and temporal) extremely arteriosclerotic. Apex-beat diffuse, outside nipple in fifth interspace. Systolic murmurs at all areas. Temperature 100° F.

The gastro-intestinal, nervous, and respiratory systems showed nothing of importance. The liver was slightly enlarged; the spleen very soft and difficult to feel, three finger-breadths below the costal margin. There was no enlargement of lymphatic glands.

Urine. Bile absent, urobilin present in large quantities. Wassermann reaction negative.

Blood count. The red cells clumped immediately in the haemocytometer, so that it was impossible to make a count. The haemoglobin was 15 per cent. Agglutination occurred at once when the blood was drawn into a syringe containing oxalate or citrate solution. When expressing the blood from the prick in the finger it was noticed that within one to two seconds the drop coagulated and serum separated. No matter how quickly a blood film was spread the cells clumped into groups of from five to fifty. This pepper-grain appearance was visible to the naked eye, and resembled the phenomena seen when incompatible bloods are mixed together. Vitally stained films showed that practically every cell was a reticulocyte, the percentage count being at least 90. This is the highest I have ever seen or read of in the literature. A stationary blood count, with 90 per cent. reticulocytes in the peripheral blood, showed that the most intense haemolysis was proceeding in the patient, and that practically the whole of the blood was being destroyed and replaced daily.

Before risking a blood transfusion I asked my assistant, Dr. John McMichael, who for the past two years has been making a special study of diseases of the liver and spleen, to investigate the phenomena of auto-agglutination, coagulation, and fragility of erythrocytes present in the patient's blood. He reported that the coagulation time of blood withdrawn from the basilic vein was under one minute (normal 10–12 minutes). Auto-agglutination occurred in the presence of anticoagulants including citrate, oxalate, and Bayer 205. If blood drawn into the syringe containing some Bayer 205 was repeatedly washed with saline, agglutination disappeared and the corpuscles formed an even emulsion. On adding the patient's serum or plasma to the washed corpuscles, agglutination reappeared. If the plasma or serum was heated to 56° C. for half an hour, so that complement was destroyed, and then added to the washed cells, agglutination occurred extremely slowly.

On searching the literature on auto-agglutination a paper by Li Chen Pien (4) was found, which clearly showed that temperature plays an important part in the production of this phenomenon. Thus auto-agglutination occurs in most animals and not infrequently in human beings, at 0° C., but disappears at blood heat. Accordingly the influence of temperature was investigated in this patient, and it was found that auto-agglutination disappeared at 37° C. and reappeared at room temperature. The absence of clumping of the red cells in the patient's circulation may thus be explained.

Fragility test. Haemolysis of the washed corpuscles started at 0.6 per cent. saline and was complete at 0.35 per cent.

Van den Bergh reaction. Direct negative; indirect positive. Icteric index 35.

The patient had brought a nephew and a niece with him from Inverness, and their blood was tested with a view to transfusion. While the blood of

the nephew was incompatible the blood of the niece appeared to be satisfactory. Nevertheless the risk of transfusion appeared very great, and it was with considerable trepidation that one c.c. of the donor's blood was injected into the patient's vein. No reaction occurred, so ten minutes later 10 c.c. were injected. Nothing further was done that day and, as no clinical signs of embolism or thrombosis had appeared, on February 4, 1932, three-quarters of a pint of citrated blood was given intravenously. Apart from a rise of temperature up to 101° F., no ill effects were noticed, and on the following day one pint of blood was given. The patient was distinctly stronger and breathing more easily. Sir John Marnoch saw the patient and decided that the operative risk was still too great, and that operation should be delayed for a few days to watch the effects of the transfusion.

On February 8, 1932, auto-agglutination was not so marked, and a fairly accurate blood count was made. The red cells numbered 750,000, haemoglobin 20 per cent., colour index 1.3. Practically every cell was a reticulocyte.

Polymorphonuclear leucocytes were 75 per cent. (including 6 per cent. eosinophils). Lymphocytes were 25 per cent. For every 100 white cells 2 megaloblasts and 8 normoblasts were found. Films showed marked anisocytosis, poikilocytosis, and polychromasia.

The clinical condition of the patient was so extremely serious that it was decided to delay operation no longer, since the only possibility of reducing the intense blood destruction appeared to be removal of the main haemolytic organ, namely, the spleen.

On February 11, 1932, Sir John Marnoch performed splenectomy. A local anaesthetic was used until the later stages of the operation, when gas and oxygen were administered. The spleen was grossly enlarged, dark red in colour, and soft in consistence, but not adherent. One pint of citrated blood from the same donor was run into the basilic vein. Fortunately the donor was a strong country girl who withstood the effects of giving nearly three pints of blood within a few days without ill effects. Throughout this trying period this young woman behaved with the greatest courage and fortitude.

On February 12, 1932, the patient's condition was satisfactory and, considering his extreme anaemia and cardiac weakness, had withstood the operation remarkably well.

On February 13, 1932, the heart began to fail, fluid collected in the serous cavities, and the patient died that night. No benefit had resulted at that date either from the splenectomy or the blood transfusion, since the blood count had fallen to: red blood-cells 470,000, haemoglobin 7 per cent.

Post-mortem Examination

A moderate amount of free fluid present in the serous cavities. Heart chambers dilated. Muscle extremely pale and anaemic. Fatty changes marked. Arteries, including splenic, renal, and coronary, showed advanced arteriosclerotic changes. Perfect haemostasis in pedicle of spleen.

Liver. Slightly enlarged and marked fatty changes present. Perl's Prussian blue reaction positive.

Kidneys. Pale and bile-stained. Capsule stripped readily. Prussian blue reaction markedly positive.

Lungs. Chronic bronchitis with oedema and congestion of the bases.

Bone-marrow (longitudinal section of femur) showed a well-marked erythroblastic reaction throughout the whole length of the shaft.

*Microscopic Appearances of Spleen and Liver. Report by
Dr. John McMichael*

The spleen was markedly enlarged (weight 820 grm). Microscopically the striking feature was the intense arterial congestion—the pulp being loaded with red blood corpuscles without marked dilatation of the venous sinuses. The adventitia of the arteries was often thickened and hyaline. This is probably a senile change in addition to the common hyaline appearance of the vessels. The appearances are those of acholuric jaundice.

Cirrhosis absent. Kupffer cells proliferated. Extensive fatty changes in the liver cells, especially at the periphery of the lobules. The principal feature is a deposit of free iron in the liver cells, and also some yellowish pigment which does not give the iron reaction—probably bile pigment. The appearances are characteristic of haemolytic jaundice.

Discussion

The nine cases of haemolytic anaemia described in the present series have certain features which resemble pernicious anaemia on the one hand and familial acholuric jaundice on the other.

(a) *Pernicious anaemia.* 1. *Colour index.* A colour index over unity was present at some period in all the cases except Case 7.

2. *Hyperchromia* was a feature of the red cells in stained films, but during haemolytic crises the intense basophilia present tended to mask it.

3. *Shape of the red cells.* An oval outline is a highly characteristic feature of the erythrocyte in pernicious anaemia in the relapse stage. Eighty per cent. of the red cells show this feature. On the whole, the macrocytes in the present series of cases tended to be more circular in outline than would be expected in a case of pernicious anaemia of similar severity.

4. *Nucleated red corpuscles.* In all cases nucleated red corpuscles were found. The majority were normoblasts, mature and immature, but undoubtedly megaloblasts were also present. The number of nucleated red cells seen during a 'blast' crisis was extremely large. In one case (Case 7) 17,000 nucleated red cells were found in each cubic millimetre of blood, a number greater than the total white cell count. The significance of a 'blast' crisis in pernicious anaemia has not been definitely settled. Generally speaking, a moderate number of nucleated red blood corpuscles may appear in the peripheral blood at the beginning of a remission, but marked blood crises are usually agonal phenomena preceding a fatal termination. In this series the 'blast' crises must be considered merely as evidence of the intense bone-marrow activity that was proceeding, and have not the same serious significance in prognosis as in pernicious anaemia. The degree and duration of the 'blast' crisis was far greater than usually occurs in pernicious anaemia.

5. *White blood corpuscles.* A reduction in the number of white cells is characteristic of pernicious anaemia, and was present at some time or other in the majority of cases in the present series. Qualitative changes of distinct diagnostic value were, however, present, since immaturity, as shown by a shift to the left in the Arneth count, was generally present. A dissociation of the Arneth count to both right and left occurs sometimes in pernicious anaemia, but the shift to the left is never so marked as that found in the present series.

6. *Bilirubin estimation.* An excess of bilirubin in the blood and faeces, and urobilin in the urine, were found in this series, as occurs in pernicious anaemia in the relapse stage. In the latter disease, liver therapy rapidly produces a reduction and a return to normal values within two or three weeks. A stationary or increasing blood bilirubin level was present in some of the cases in the present series for many months at a time, in spite of intense liver therapy.

7. *Response to treatment.* A rapid response to liver therapy, indicated by a reticulocyte crisis and a rise in the red cell count and haemoglobin level, is one of the most characteristic features of pernicious anaemia. The failure of the cases reported in this series to respond to massive and long-continued doses of liver, liver extract and ventriculin, is therefore of great diagnostic and prognostic value.

8. *Fragility test.* The erythrocytes in the present series of cases showed normal or increased fragility. In no case was there an increased resistance to hypotonic saline, as is commonly found in cases of pernicious anaemia.

9. *Gastric secretion.* In the majority of cases in the present series free hydrochloric acid was present, a point of great importance in the differential diagnosis.

10. *Splenomegaly.* Enlargement of the spleen was present in every case reported in this series. A palpable spleen is found in less than 50 per cent. of cases of pernicious anaemia, and the degree of enlargement, when present, is comparatively small. Splenomegaly of the magnitude present in this series of cases is strongly against the diagnosis of pernicious anaemia. Microscopic examination of the spleen, removed *post mortem* or at operation, showed that the features regarded as characteristic of pernicious anaemia were present in only two of the nine cases reported.

11. *Reticulocyte counts.* In the relapse stage of pernicious anaemia the reticulocyte count is low, but rises rapidly a few days after liver treatment has been started. Concomitantly the red cell and haemoglobin level rises, and alterations, quantitative and qualitative, in the white cell picture and bilirubin, occur. In the present series of cases, in spite of reticulocyte-percentage counts from 25 to 90 per cent., the blood level remained stationary for weeks and months, or in some cases actually fell. The balance between blood formation and blood destruction is most easily and accurately measured by estimating the reticulocyte-percentage count and the blood level at intervals over a period of time. In the present series of cases the

severe anaemia was due to intense blood destruction, which the bone-marrow vigorously attempted to compensate. In pernicious anaemia the essential cause of the anaemia is defective blood formation due to a deficiency of the blood-maturing factor present in liver, while blood destruction is of minor and secondary importance.

(b) *Acholic jaundice*. The essential diagnostic features of acholic jaundice may be summarized as follows: family history; hypochromic microcytic anaemia; fragility of the erythrocyte; splenomegaly and the evidences of increased blood destruction, as already described.

A congenital tendency to icterus or anaemia was not obtained in any of the cases reported. It is suggested that the term acholic jaundice should be reserved for the familial form of haemolytic anaemia. A high colour index was present at some period in every case except Case 7. It should be noted that in recent publications on familial acholic jaundice colour indices over unity and megaloblasts in the peripheral blood have been reported as being present during severe haemolytic crises. Fragility of the erythrocytes was normal, except in Cases 1, 7, and 9. This apparently does not rule out the diagnosis of familial acholic jaundice, if some of the recent published work is accepted, since 10 per cent. of cases are said to have normal fragility. Gross splenomegaly was present in every case in the present series. The microscopic appearance of the spleen in familial acholic jaundice is now so well recognized that it may be said to be pathognomonic. It was only found in Cases 7 and 9. Case 8 is still alive and has refused operation. The most characteristic feature of acholic jaundice is the combination of signs of excessive blood destruction and active blood formation. A high icterus index, an indirect van den Bergh reaction, excessive quantities of bilirubin in the faeces and urobilin in the urine, representing blood destruction on the one hand, and a high reticulocyte-percentage count continuing over considerable periods of time with little or no change in the blood level, representing active erythropoiesis on the other, are the essential criteria on which to base a diagnosis of the haemolytic anaemia occurring in acholic jaundice. These features were found in every case in the present series. Cases 7, 8, and 9 appear to be examples of the acquired form of acholic jaundice, as judged by the clinical and haematological picture, and by the microscopic appearance of the spleen. The Price-Jones curve showed a different form in these cases to that seen in Cases 1 to 6. In Cases 7 and 8 the peak of the curve was shifted to the left, the majority of the cells measuring 6.5μ . In Case 9 the peak fell within normal limits. The base of the curve was considerably broadened in Cases 7 and 8, the cells varying from 4 to 10μ , and in Case 9 from 4 to 11.5μ . Measurement of the diameters of the erythrocytes therefore revealed that macrocytosis was not really a prominent feature of these three cases, although microscopic examination of the stained film appeared to show this to be the case. The degree of microcytosis present made the cells with diameters of 8 to 9μ appear excessively large. In short, the apparent

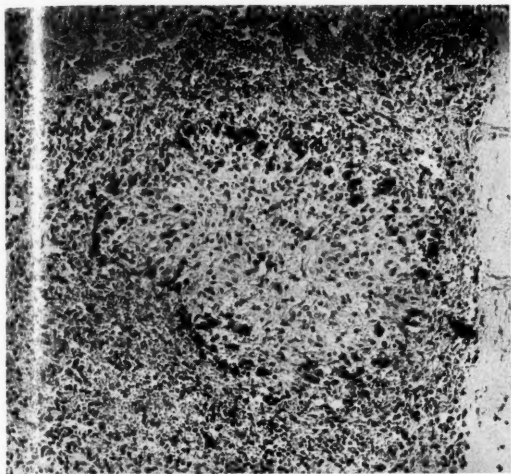
excessive macrocytosis was in the nature of an optical illusion. Cases 7, 8, and 9 appear to me to present certain features which enable us to understand how blood formation will proceed to revert towards the embryonic megaloblastic type, if excessive strain on the bone-marrow is allowed to continue for long periods. Case 7 was an acquired haemolytic anaemia occurring in a young man, which was treated during the early stage by splenectomy. The degree of anaemia was extremely severe (750,000 red cells per cubic millimetre) but the duration was short. An occasional megaloblast was found, but the colour index was low. Case 8 had a severe haemolytic anaemia for months; megaloblasts were present and the colour index was over unity until a natural remission allowed the blood level to rise. Case 9 had been severely anaemic for two years. A blood count around one million had been present for approximately one year. Megaloblasts were present, the colour index was consistently over unity, and the Price-Jones curve showed that a broadening of the base and a shift to the right were occurring.

Cause of the intense blood destruction. In Cases 1, 2, and 3 the haemolytic anaemia was due to Hodgkin's disease. Whether the haemolysis was consequent on the infiltration of the bone-marrow with microscopic deposits of lymphadenomatous tissue, or to over-activity of the affected spleen, is a problem which has already been discussed and which at present cannot be said to be settled. In Case 4 the haemolytic process was due to lead poisoning, and its exact mechanism is not understood. In Cases 5 and 6 no explanation for the blood destruction is available. In Cases 7, 8, and 9, which are forms of acquired acholuric jaundice, it is presumed that some acquired defect in the formation of erythrocytes occurred, which made them more susceptible to destruction by the reticulo-endothelial system of the body, particularly in the spleen.

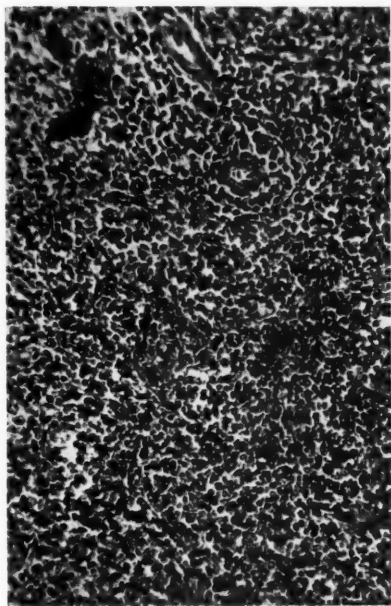
I desire to express my thanks to the following physicians for allowing me to examine and report on cases under their charge: Dr. Goodall, Dr. Hewat, Dr. Croll, Dr. Reid, and Dr. McDonald.

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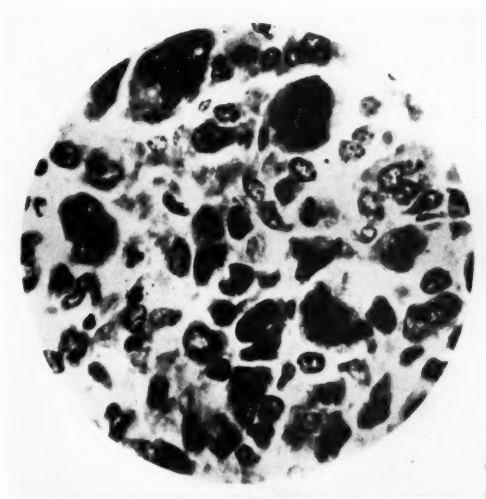
Case 2. Avascular lymphadenomatous nodule
in spleen



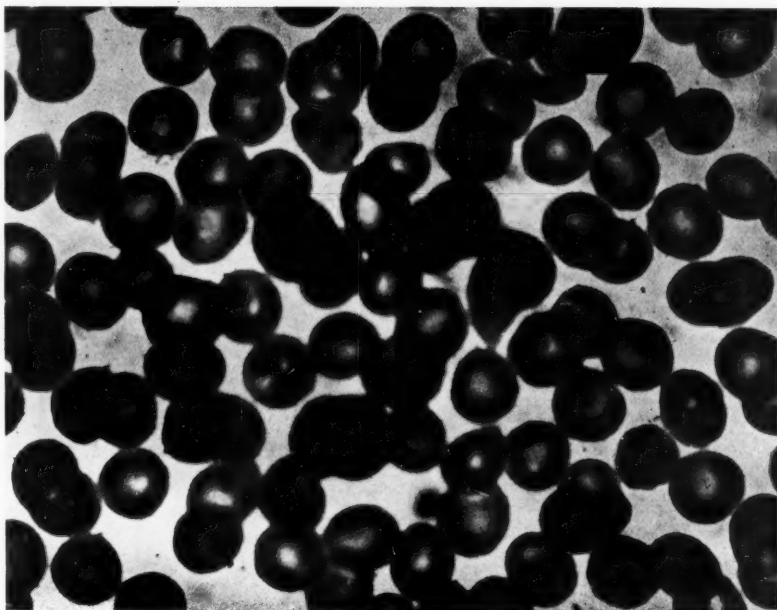
Case 7. Spleen



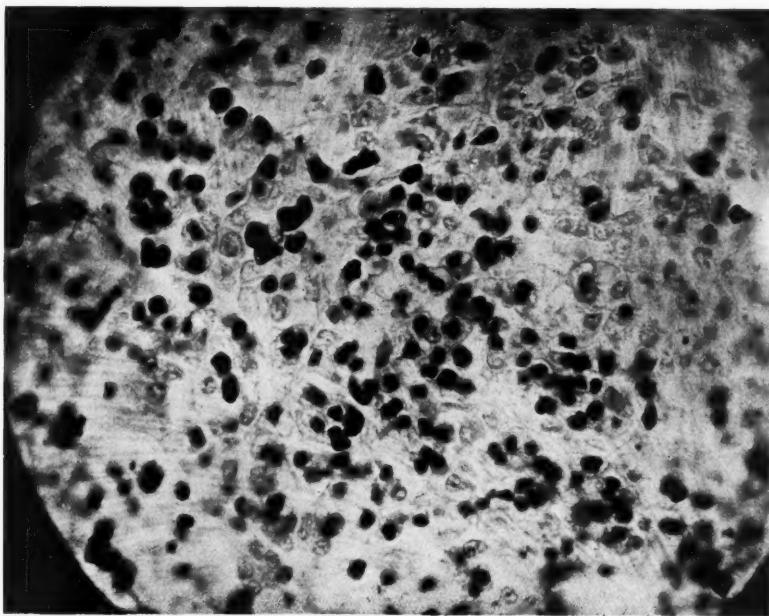
Case 6. Spleen



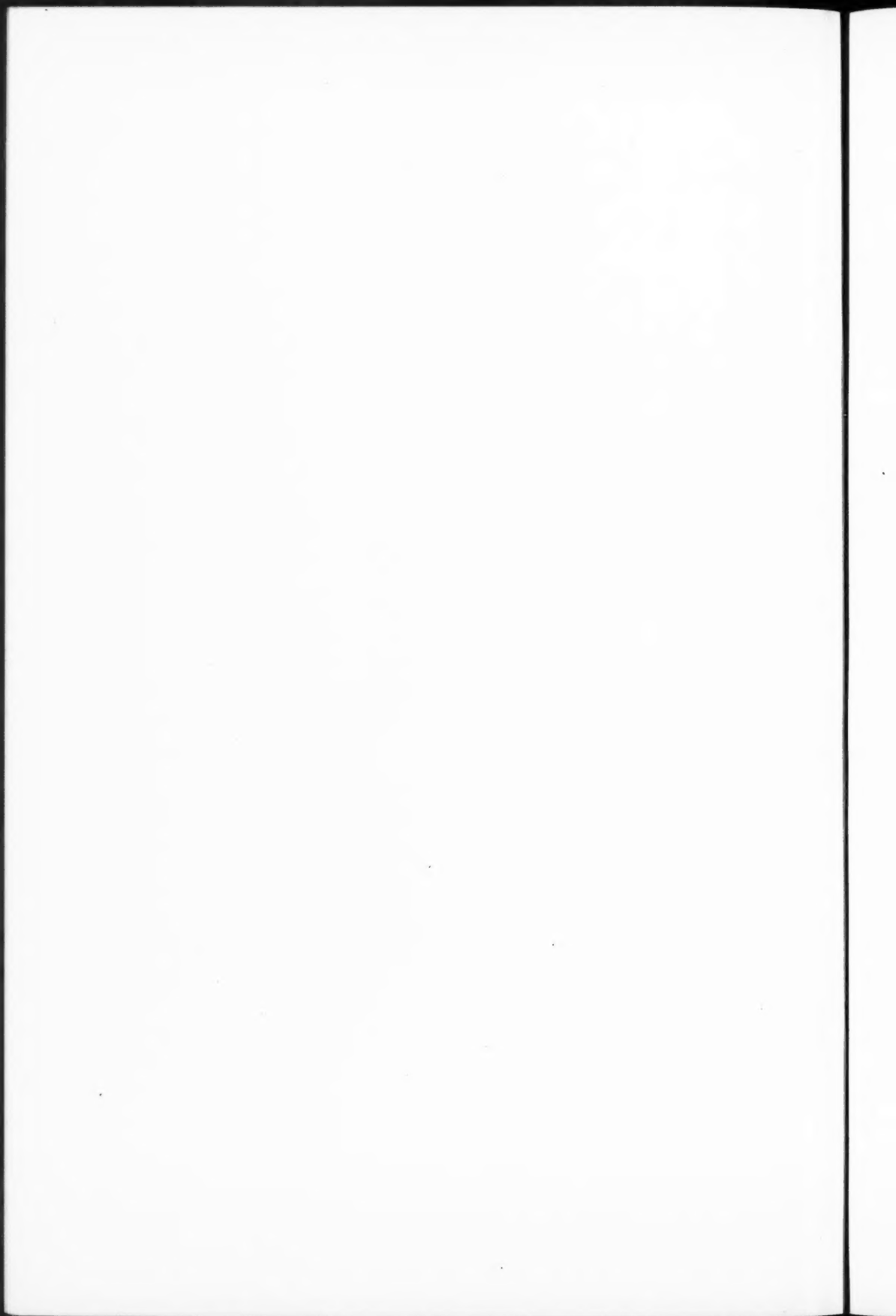
Case 1. Lymphadenomatous tissue in lymphatic
gland



Case 5. Double film to show macrocytosis. Dark cells belong to patient, other cells normal



Case 5. Myeloid metaplasia in spleen



PERMANENT ORGANIC CARDIOVASCULAR DISEASE AFTER THYROTOXAEMIA¹

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Introduction

THE following investigation was undertaken with the object of throwing light upon the question whether hyperthyroidism could be a direct and only cause of permanent organic cardiac disease. The close association between hyperthyroidism and cardiac failure is too generally accepted to need especial mention, but the manner of production of the heart failure is less understood. The possibilities are three. The prolonged tachycardia may be the cause of this. The thyrotoxin may exert a directly toxic action upon heart-muscle, in which case, of course, the tachycardia would be a subsidiary factor. The tachycardia, or thyrotoxicity, or both, may produce permanent damage only on hearts already affected by, or predisposed to, injury by the other known causes of heart failure, such as rheumatism, syphilis, and arteriosclerosis. If the latter conjecture were true, normal hearts would not be permanently affected by thyrotoxicity.

In the literature we have been able to find few references to this problem. Parkinson and Cookson (2), in a recent paper, mention a number of published papers on thyrotoxicosis and cardiovascular disease, and Paul White (1) refers to the condition in his recent work *Heart Disease*. Also the subject is discussed by Jenner Hosken in Joll's newly published book on diseases of the thyroid gland (3). Cardiac enlargement is, in the opinion of the majority of writers, a common sequel to thyrotoxicosis. That this enlargement is the result of persistent tachycardia caused by the presence of hyperthyroidism is the opinion of White, Lahey (4), and others working on this subject. Wilson and Goodall (5) consider that the condition of thyrotoxicosis is associated with specific changes in the heart-muscle, producing a myocarditis which can be seen in the round-cell infiltration, &c., which they have described in the microscopical material obtained at autopsy. The answer to the question as to whether hyperthyroidism produces permanent myocardial changes should be found in an investigation of the cardiovascular condition of patients who suffered from the disease in the past, were treated, and so became free from symptoms of thyrotoxicity.

¹ Received July 12, 1932.

We have been unable to find in the literature reference to any such series, with the exception of that of Lahey (4). This writer, in a paper published in 1929, entitled 'End Results in Thyrocardiacs', gives some evidence on these points. 138 cases of 'thyrotoxicosis', manifesting some degree of cardiovascular involvement, were operated upon. Ninety-three of these, at the time of operation, showed signs of congestive failure. 85.9 per cent. of the cases were fibrillating. The average duration of 'heart symptoms' prior to operation was $2\frac{1}{2}$ years. Of 101 cases traced and alive $3\frac{1}{2}$ years after operation, 2 were completely disabled, 4 partially disabled, and 95 had returned to normal life. The age-distribution of their cases was as follows:

Aged 20-29	1
30-39	17
40-49	37
50-59	56
60-69	27
70-75	4
	<hr/> 142

From this experience Lahey concluded 'that thyroidism does not cause heart disease', but that the signs of heart failure are due to the effect of 'thyroidism' on a heart which is already damaged and unable to withstand the excessive burden of the superimposed drive of hyperthyroidism. His records show that heart failure when associated with 'thyroidism' occurs commonly in middle-aged people, but rarely in young people. His investigation, by using disablement as the criterion, would seem to some extent to fail to reach the root of the matter. For if thyrotoxicosis were to produce a permanent myocardial change which was slight only, this might not be revealed by symptoms alone within $3\frac{1}{2}$ years; whereas enlargement of the heart would almost certainly be present. It is interesting to observe, however, that his conclusions coincide closely with those reached in the present communication.

Cabot (8) emphasizes the fact that cardiac failure is rare in the acute exophthalmic goitre of young persons; 'even when the organ seems actually driven to death', there is usually no sign of passive congestion before death or at necropsy. It is usually a 'toxic and not a congestive death'.

The pathological observations in cardiovascular disease and thyrotoxicosis consist in great part in post-mortem records on cases of thyrotoxicosis which, during the active phase of the disease, have died. Fahre and Kuhle (7) found macroscopic changes, such as enlargement, in fifteen out of eighteen cases with Basedow's disease, and in eight cases of colloid goitre with cardiac symptoms. Willius, Boothby, and Wilson (10) found hypertrophy of the heart to be present in a large percentage of the cases that they observed at autopsy. Symmers (9) described six cases of cardiac hypertrophy which he considered to be secondary to thyroid disease. After reading through his case records we felt that rheumatic heart disease, syphilis, and coronary

disease and high blood-pressure were probably the underlying aetiological causes. Goodpasture (6), at autopsy, found histological changes in the heart-muscle of patients dying of goitre. He found an acute necrosis, similar to that associated with the extreme intoxication of acute fevers. Parkinson and Cookson (2), in forty-three necropsies on goitre cases, found cardiac enlargement in 50 per cent. In brief, the material that has been examined is nearly all obtained from autopsies on persons dying with clinical evidence of thyrotoxicosis. It is possible that death was due to the effect of thyrotoxicosis on a previously damaged heart.

Method of Investigation

The points in the present investigation upon which attention was especially focused were as follows: Cases were investigated who had suffered from thyrotoxaemia at a former period, who were treated, generally by surgical means, and who, since their treatment, had enjoyed a period of freedom from obvious hyperthyroidism. It was felt that an interval of time was necessary before the coincident effect of thyrotoxaemia on the heart could be separated from the permanent or ultimate effect. The severity of the disease, its duration, and its date of operative control, were noted.

Evidence of present thyroid activity was searched for, and valuable confirmation as to this point was obtained by consultation with Professor F. R. Fraser and Mr. T. P. Dunhill, who were following up the same cases from a more general point of view.

The present state of the heart was thoroughly investigated from the point of view of symptoms of heart failure, dyspnoea, orthopnoea, pain, constriction, palpitation, exhaustion, cough, giddiness, syncope, and oedema; and of physical signs, such as dyspnoea, orthopnoea, cyanosis, pallor, pulsation, clubbing, tremor. The pulse-rate and rhythm and the systolic and diastolic blood-pressure were also investigated. The position of the apex-beat was measured. The presence of thrills, abnormal heart sounds, and hyperaesthesia was investigated. A 6-foot X-ray film, for measurement of the heart-chest ratio, was taken in all cases. An electrocardiogram was taken in every case. In addition careful attention was directed to the aetiology of the cardiac condition and the history as to rheumatic fever, acute rheumatism, sore throats, chorea, scarlet-fever, diphtheria, and other diseases was carefully taken.

The cases were on the whole of a severe type, owing to the fact that pressure on the available bed-space had originally caused only the severest cases to be admitted and treated. The interval of time between their discharge from hospital and their being reinvestigated was, in some cases, as long as nine years. Not every patient written for responded, for some in the meantime had died, others had moved to too great a distance to return for examination, and others had been lost sight of.

Taking the analogy of known cases of myocardial disease, such as rheumatism, syphilis, and arteriosclerosis, it is probable that signs of heart disease would appear in a definite percentage of a similarly selected series of patients.

The cases examined are divided into two groups. Group I consists of thirty-two cases of treated hyperthyroidism who were first admitted to Professor Fraser's or Mr. Dunhill's beds in 1922-3. These were written for in 1929 and 1930, irrespective of the presence or absence of any cardiac lesion at the time of first admission.

Owing to the comparatively small number in this series showing evidence of cardiac enlargement at the time of re-examination a second series (Group II) was added. In this group were cases from the same source, who had had convincing evidence of cardiac disease at the time of their admission between 1924-7 inclusive. There were ten of these in all, two had died, two wrote from a distance, and of two there was no news. Thus the total number of cases from which deductions can be drawn is thirty-six. All cases were treated surgically by partial thyroidectomy except one (Case 33) who recovered after prolonged medical treatment.

GROUP I

Analysis of Thirty-two Cases of Treated Hyperthyroidism

This group of cases was subdivided into four sub-groups: A. Cases showing evidence of active thyrotoxicity. Of five cases (1-5) three had hearts of normal size, one had marked left ventricular enlargement and auricular fibrillation, and one had a slight left ventricular enlargement. B. Cases with normal hearts; nineteen cases. C. Cases with enlarged hearts, but in whom an obvious cause of cardiac enlargement was present. D. Cases with enlarged hearts, in whom no obvious cause of cardiac enlargement was present.

It is obvious that the cases in Group A are outside the present argument, that the cases in Groups B and C form a valuable control group, and that the cases in Group D constitute the crux of the problem and require the fullest clinical details in order to shed light on the question as to whether thyrotoxicity can of itself cause permanent cardiac disease.

C. *Cases with enlarged hearts in whom a known cause for the enlargement was discovered.* Eliminating the nineteen normal cases, there remain eight (Cases 25-32) with evidence of cardiac enlargement. Two of these present evidence of rheumatic carditis and two of hyperpiesis and arteriosclerosis. Particulars of these four cases are as follows:

Case 25. H. U., male, aged 28. Was first seen in the Out-patient Department in January 1921 at the age of 17.

He had suffered during the preceding two years from rheumatic pains in the limbs and for the preceding few months from palpitation, nervousness, and a swelling in the neck.

On examination he showed signs of exophthalmic goitre and of marked tonsillar infection. The heart showed at this time a diffuse cardiac impulse widely visible over the third, fourth, and fifth spaces; the apex-beat was very forcible and there was a soft systolic murmur at the apex and not at the pulmonary base.

In May 1921 a partial thyroidectomy was performed, and during convalescence he developed diphtheria. Some thyrotoxaemia remained, for which two further partial thyroidectomies were performed, one in October 1921 and the third in January 1926. The section of the gland was typical of Graves' disease.

In December 1925 large septic tonsils were removed. In 1925 the basal metabolic rate was +44 per cent. and in 1926 +56 per cent.

In 1925, eight years after thyroidectomy, aged 25, he was at work in a cable works and was in reasonably good health.

The heart impulse was visible in the fourth, fifth, and sixth space. The apex-beat was slightly increased in vigour, and was palpable in the mid-clavicular line in the sixth space. There was a systolic murmur at the apex conducted into the axilla, and having the other characteristics of mitral regurgitation. The electrocardiogram showed well-marked right-sided predominance. The blood-pressure, lying and standing, was 160/90.

Comment. The history and signs indicated the presence of a rheumatic carditis of long standing. Other aetiological points of interest were the prolonged and severe tonsillar sepsis and the attack of diphtheria. There was also a definite hyperpiesis, if his age (25) is taken into consideration.

Case 26. E. P., female, aged 59. This woman attended the Out-patient Department with Graves' disease first in 1921, at the age of 48. She had then been suffering from enlargement of the neck, palpitation, tremor, and a feeling of warmth for five years. The heart at this time was said to be hypertrophied and there was a systolic murmur present at the apex. The tonsils were inflamed and colds with hoarseness were common at that period.

She remained fairly well able to attend to her business until January 1928, when she was admitted for medical treatment. The heart still showed enlargement, due to hypertrophy and dilatation, with a coarse systolic thrill and a harsh systolic murmur at the apex, the latter conducted to the axilla. The tonsils were removed during this admission. The basal metabolic rate was +61 per cent., and the electrocardiogram showed left-sided predominance and auricular fibrillation.

In March 1928, she was transferred to a surgical ward, and a partial thyroidectomy was performed by Mr. Dunhill. The microscopic section showed the changes typical of toxic goitre.

In May 1928, she was readmitted with dyspnoea, swelling of the feet, legs, and abdomen. The heart was even more enlarged, the apex-beat being in the sixth space, six inches from the midline to the left. Besides the systolic murmur previously present, there were now a rumbling diastolic murmur and a slight diastolic thrill restricted to the mitral area, typical of mitral stenosis with auricular fibrillation.

Under digitalis the rate was fairly well controlled, and the signs of congestive failure disappeared. She was discharged with a basal metabolic rate of +25 per cent.

The improvement was maintained, but not free from symptoms, for

palpitation and undue fatigue were still present, until April 1929, when she was re-admitted and a second partial thyroidectomy was performed.

As a result she was much improved as regards the tremor and nervousness. For a short period the heart showed the presence of auricular flutter, but she was discharged with fibrillation. The cardiac condition remained practically unchanged.

On August 15, 1929, there was still marked left ventricular hypertrophy; the electrocardiogram showed left-sided predominance and auricular fibrillation, and the six-foot X-ray plate showed a heart-chest ratio of 0.6. The heart-shadow was increased in width with rather a flat left border. There was a harsh, loud systolic murmur at the apex conducted towards the axilla. The blood-pressure was 180/100, as nearly as could be judged in the presence of the fibrillation.

Comment. The character of the murmurs alone is conclusive of a mitral stenosis with some insufficiency. There appeared to be little doubt that this patient had a rheumatic carditis. Other factors to be remarked upon are the severe tonsillar sepsis and the hyperpiesis.

The following two cases (Cases 27 and 28) show evidence of hyperpiesis; one had other signs of arteriosclerosis.

Case 27. L. F., female, aged 57. This patient had had a somewhat enlarged neck since childhood. At the age of 44 she began to suffer from nervousness, tremor, and loss of weight. This continued, and four years later she suffered from palpitation, shortness of breath, and further loss of weight.

In 1925, at the age of 50, she underwent two operations for partial thyroidectomy. At that time exophthalmos was marked; the heart was said not to be enlarged; the basal metabolic rate before the first operation was + 69 per cent.; the histological examination of the removed tissue showed changes typical of exophthalmic goitre.

She improved considerably, although unable to do much work as a char-woman, until in 1928 a further swelling in the neck appeared. Palpitation, tremor, and further loss of weight occurred, and dyspnoea was increased.

In April 1929, a third operation was performed, after which she was improved considerably.

In August 1929 there were no signs of thyrotoxicity, but exophthalmos was still present. The heart showed a regular rhythm and a rate of 72. Fibrillation had never been observed. The apex-beat was displaced slightly to the left in the fifth space. The cardiac impulse was rather forcible. The first sound was accentuated at the apex. The electrocardiogram showed no left-sided predominance or other abnormality. The X-ray examination showed a slight increase in the heart-chest ratio, - 0.55. The blood-pressure was 180/100. The radial arteries were slightly thickened and tortuous.

Comment. The enlargement of the heart is shown to be slight, and is not out of proportion to the hyperpiesis and arteriosclerosis present. It is to be remembered that thyrotoxaemia in this case was still present up to four months before the final evaluation.

Case 28. A. B., female, aged 48. At the age of 39 began to suffer from breathlessness, and a year later from fullness in the neck. Five years later exhaustion became marked, with nervousness, palpitation, and oedema of the feet.

She was admitted in 1928 with a basal metabolic rate of +36 per cent. and signs of hyperthyroidism. She weighed 6 stone 12 pounds. The cardiovascular symptoms and signs were marked, the heart being enlarged and auricular fibrillation being present. The feet and legs were swollen on admission. In the same year two partial thyroidectomies were performed with an interval between.

After the second operation she was greatly improved, the signs of thyrotoxaemia disappearing and the basal metabolic rate falling to -10 per cent. Auricular fibrillation still persisted, and in the electrocardiogram 'T' was inverted in Lead III (Fig. 1).

She then resumed her secretarial work and remained in good health until she was seen in 1930, two years later. She was then rather adipose, having nearly doubled her weight (12 stone 8 pounds). There were no signs of thyrotoxaemia. The heart-rate was 112, auricular fibrillation was present, but there was no electrocardiographic evidence of left-sided predominance. The apex-beat was difficult to localize. The X-ray showed a heart-chest ratio of 0.57, the heart being slightly enlarged to both left and right. The right auricle and superior vena cava were noticed to be enlarged. The blood-pressure averaged 180/110, as nearly as could be measured.

Comment. The effect of the thyrotoxaemia in this case had been markedly cardiovascular at the time. The present findings showed a slightly enlarged heart, the enlargement not being more than could be easily accounted for by the hyperpiesis, together with the auricular fibrillation. That the electrocardiogram showed no left-sided enlargement is significant.

Thus, in recapitulation, Cases 25 to 28 all show cardiac enlargement. But in every case a definite cause is present, other than the thyrotoxaemia. The evidence for rheumatic heart disease in Cases 25 and 26 and for hyperpiesis in Cases 27 and 28 is conclusive. It is interesting to observe that even in the two rheumatic cases some hyperpiesis was present. Moreover, the interval between the final thyroidectomy and the final complete examination was short; in Case 26 this was only four months, in Case 27 four months, and in Case 28 two years.

D. *Cases with enlarged hearts in whom no obvious cause for the enlargement was discoverable.* There were four cases. These were first examined in 1929 and 1930, but their detailed examination was so important that they were reinvestigated in 1932 with even greater care. If these cases were to give no sign of any other cause for cardiac enlargement, then the case that this was due to thyrotoxaemia would be a strong one. The converse argument is equally valid.

Case 29. G. D., female, aged 30. First noticed swelling of the neck in 1917, when she was aged about 15. This gradually increased in size. At the age of 16 some dyspnoea and tachycardia became noticeable. These

symptoms increased, and at the age of 20 they were present even on walking. She lost 25 pounds in weight between the ages of 17 and 20.

In March 1921 she received some medical treatment, and the tonsils were removed, for she had suffered from frequent attacks of tonsillitis since early childhood.

In 1922 she was admitted with the classical signs of Graves' disease. The basal metabolic rate was +67 per cent. The heart at this time showed some enlargement, the apex-beat being $4\frac{1}{2}$ inches from the midline and $\frac{1}{2}$ inch outside the nipple-line. No murmurs were present. Two partial thyroidectomies were performed, with a month's interval. A section of the gland showed changes typical of exophthalmic goitre.

She remained in fair health, doing housework, until she was seen in 1929. Slight dyspnoea, especially on climbing stairs, was still present, and walking was limited, as her breath was rather short.

On examination there were no signs of hyperthyroidism. There was no obvious dyspnoea, cyanosis, or pallor. The pulse-rate was 80. The heart showed some evidence of left ventricular hypertrophy, for the impulse was definitely forcible, had a sustained thrust, and was $\frac{1}{2}$ inch outside the nipple-line. The first sound at the apex was accentuated. No murmurs were present.

The blood-pressure was 150/100 (several determinations). The arteries were not abnormally palpable or tortuous.

The electrocardiogram tracing showed some slight evidence of left-sided predominance. The X-ray showed a heart-chest ratio of 0.6, the heart being definitely slightly enlarged, especially to the left.

The centrifugalized specimen of urine showed no casts or red blood-cells. There was no albumin.

Unfortunately the patient left no known address and has not been traced.

Comment. The cardiac enlargement was present at the time of the thyroidectomies eight years previously. It is shown by X-ray to involve both right and left sides and is associated with a definitely raised blood-pressure. There seems to be no discoverable cause for this hyperpiesis, for renal disease is absent, and the age is only 27. The other factor in the history is the repeated tonsillitis in late childhood. The cardiac enlargement is possibly out of proportion to the hyperpiesis present.

Case 30. H. W., female, aged 52. First noticed palpitation and some exophthalmos in 1918 at the age of 39. She continued her work until November 1921 when she received some medical treatment. About this time she became considerably worse, losing 14 pounds in seven months. Dyspnoea and dysphagia were also present when she was admitted for partial thyroidectomy. The first was done in April 1922, the section showing the changes typical of exophthalmic goitre. At this time the heart was said to be of normal size, and with normal sounds. The basal metabolic rate before the second operation, which was done in November 1923, was +38 per cent.

The heart in October 1923 was said to be normal in size, but the first sound was accentuated.

The only event of any significance discovered in the past history was scarlet fever.

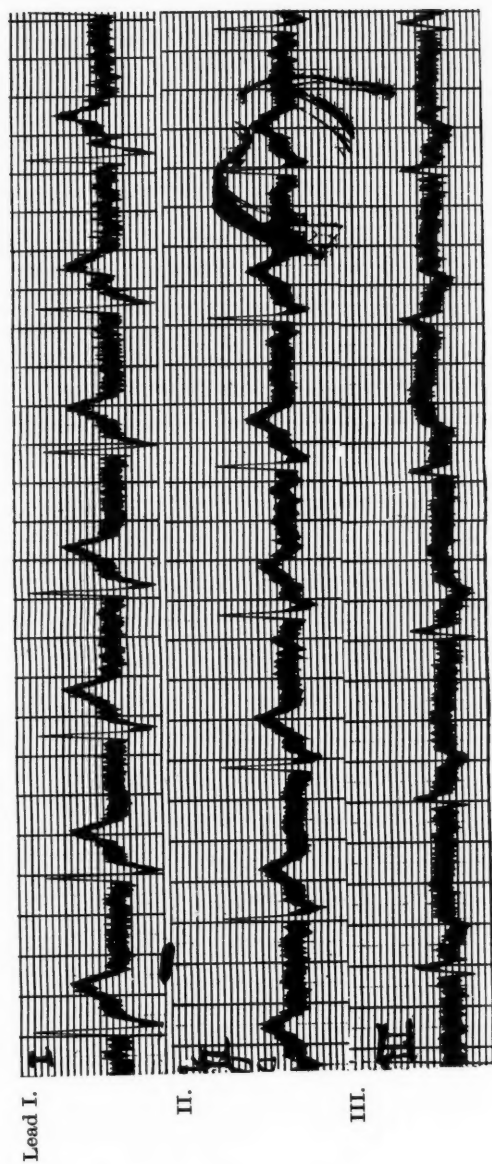


Fig. 1.

In 1929, at the age of 50, there was no evidence of thyrotoxicity. The heart gave the following physical signs. The apex-beat was in the nipple-line in the fifth space; the first sound was reduplicated at the apex in the recumbent position. The blood-pressure was 140/100 (several determinations), both lying and standing. The electrocardiogram showed very slight evidence of left-sided predominance. (Fig. 1.)

The X-ray showed some slight enlargement of the heart to the left, the heart-chest ratio being 0.61.

She was re-examined in 1932, at the age of 52. Symptomatically she was perfectly well and leading a normal life. Her appearance was slightly plethoric and she had put on weight. The heart clinically was unchanged, the first sound being still not quite clear. The electrocardiogram showed very slight evidence of left-sided predominance, and the X-ray some enlargement of the heart, especially to the left, the heart-chest ratio = 0.62. The blood-pressure being 160/100.

Comment. The increase in the size of the heart was slight; it was not accompanied by symptoms. There was apparently a developing hyperpiesis. It was not possible to say definitely whether the slight cardiac enlargement was due to the old thyrotoxicosis or to the early hyperpiesis, or both.

The absence of symptoms was possibly in favour of the latter theory, but the enlargement was out of proportion to the degree of hyperpiesis.

Case 31. F. J., female, aged 38. Complained first of nervousness and palpitation in 1921, at the age of 21. Three months later the neck became swollen. In 1922 she came to the Out-patient Department with tremor, tachycardia, exophthalmos, and an enlarged thyroid. The right ear was discharging at this time, for she had suffered severely from chronic suppurative otitis media since 1913. The heart showed the following signs: the apex-beat was $3\frac{1}{2}$ inches from the midline in the fifth space, and there was a harsh pulmonary systolic murmur. Two months after this, auricular fibrillation was present.

In August 1922 she was admitted for a course of medical treatment. The tonsils, which were very septic, were removed. She improved considerably, the basal metabolic rate falling from +48 per cent. to +3 per cent. before discharge. The auricular fibrillation stopped soon after admission. The heart during this admission was slightly enlarged, the apex-beat being 4 inches from the midline in the fifth space. The sounds were normal. There was no evidence of endocarditis. The blood-pressure was 140/75. The electrocardiogram showed marked left-sided predominance.

In January 1923 she was re-admitted with auricular fibrillation. The dyspnoea had become more severe, and swelling of the feet had been present. The basal metabolic rate was +39 per cent. The cardiac condition was identical with that at the time of the previous admission, there being some slight left ventricular enlargement. The blood-pressure now was 150/70.

In February 1923 a partial thyroidectomy was performed. She was discharged greatly improved, and with a normal basal metabolic rate.

In July 1929, at the age of 35, she still suffered from some dyspnoea and palpitation after exertion, even when walking on the level, but was able to do housework. On examination no sign of thyrotoxicity was evident. The

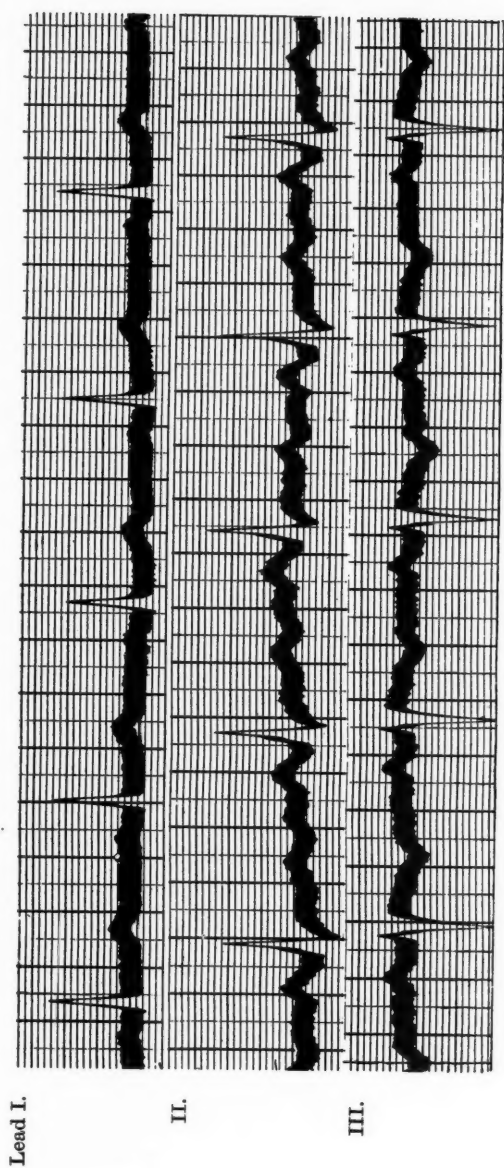


FIG. 2.

apex-beat of the heart was in the nipple-line, but the impulse was not forcible. The first sound was slightly accentuated. The blood-pressure was 125/80. The electrocardiogram showed marked left-sided predominance. The X-ray showed a heart-chest ratio of 0.50, the left ventricle being rather prominent.

In February 1932 she was re-examined. There was still some slightly diminished exercise tolerance, dyspnoea being present on over-exertion or on walking too fast. No palpitation was present. Aural discharge was still complained of. The heart showed some slight enlargement, the apex-beat being $3\frac{3}{4}$ inches to the left, in the fifth space. There was no evidence of endocarditis. The blood-pressure was now 138/92. The electrocardiogram showed well-marked left-sided predominance and the X-ray showed enlargement of the left ventricle, the heart-chest ratio being 0.54.

Comment. The very definite cardiac enlargement in this case was not to be ascribed to any known aetiological factor. It seemed to be increasing, and the increase had progressed slightly during the previous three years. The 'T' wave, having been upright, became inverted in Lead III. (Fig. 2.)

There was no evidence of a rheumatic aetiology, the most likely one at the age of 27, and there was no sign of hyperpiesis. In this case thyrotoxicity as the aetiological factor could not be excluded.

Case 32. S. H., male, aged 46. In 1922 first noticed palpitation. After six months swelling of the neck appeared. Four months later swelling of the feet was noticed. In August 1923 he came to the Out-patient Department with the signs of exophthalmic goitre. The heart was enlarged, the apex-beat being $4\frac{3}{4}$ inches to the left in the fifth space. The rhythm was completely irregular. There was a systolic murmur at the apex.

In September 1923 he was admitted to hospital. The heart had returned to the regular rhythm, but still showed enlargement of the left ventricle, the apex-beat being palpable $4\frac{1}{2}$ inches to the left in the sixth space. There was a systolic apical murmur. The blood-pressure was 150/75. The electrocardiogram was normal, when he was first admitted, but later showed auricular fibrillation. There was no left-sided predominance. The basal metabolic rate was, in October, +54 per cent.

In November 1923 he was transferred to the surgical ward. After two preliminary ligations, partial thyroidectomy was performed. The section showed changes of exophthalmic goitre, but was atypical, for many of the vesicles were normal. On discharge the heart still showed auricular fibrillation.

In April 1924 he was readmitted. Some thyrotoxaemia was still present. The heart was still enlarged, the apex-beat being 4 inches to the left in the fifth space. The rhythm was now normal. The basal metabolic rate was +14 per cent. A further partial thyroidectomy was performed.

In May 1924 the heart was less enlarged, the apex-beat being $3\frac{3}{4}$ inches to the left in the fifth space. The rhythm was now regular. The basal metabolic rate was normal.

In 1929 he felt well, could walk many miles, and was in strenuous work as a packer. The heart had a rate of 70. The apex-beat was internal to the mid-clavicular line. The electrocardiogram was normal, there being no

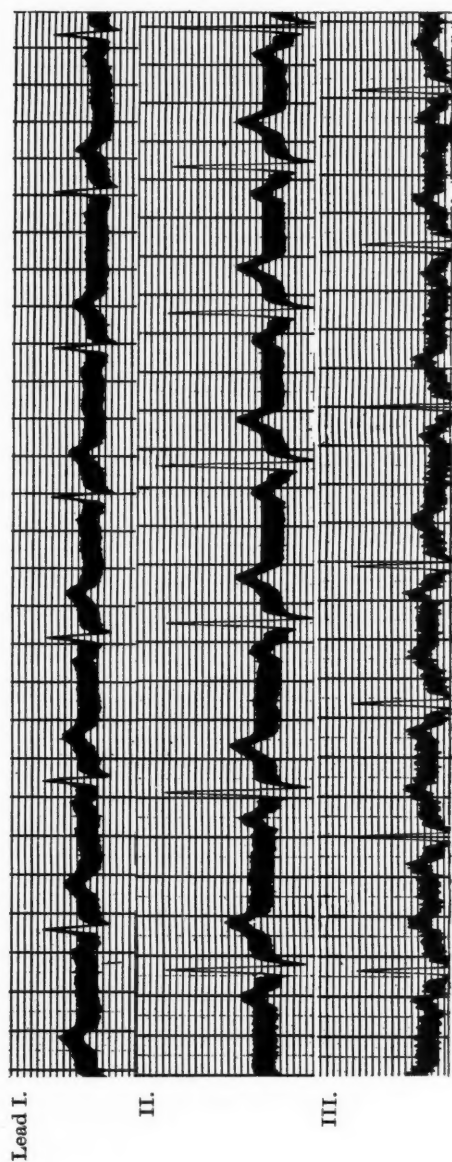


FIG. 3.

predominance. (Fig. 3.) The orthodiagram showed a heart-chest ratio of 0.53, the heart being thus slightly enlarged. The blood-pressure was 130/90.

In 1932 no symptoms were present. The electrocardiogram was normal and the orthodiagram showed a heart-chest ratio of 0.51.

Comment. This was a case where the signs of heart failure were early and marked. No other aetiological factor was found to account for these. The heart has been left with no functional disability. The structural change was definite, but the enlargement, which was originally considerable, has progressively diminished since the hyperthyroidism. Between 1929 and 1932 this diminution in size was continuing, as shown by the heart-chest ratio. The diminishing enlargement would indicate an original thyrotoxic cause, and would suggest a transient rather than a permanent cardiac lesion.

Group II

This group consists of four patients who showed signs of severe myocardial disease at the time of their thyroidectomy. They are used as subsidiary evidence of the type of cardiac disease present in hyperthyroidism and following it.

Of ten cases whose after-history was inquired into, two were dead, two wrote from a distance stating that they were well, and from two more there was no reply.

Case 33. E. M., Female, aged 52. Came first to the hospital at the age of 41 with symptoms referable to an ovarian tumour, which was removed in October 1921. In May 1922 she was found to have Graves' disease. The heart was then slightly enlarged, the apex-beat being $4\frac{1}{2}$ inches to the left in the fifth space. A systolic murmur, not conducted, was audible at the apex.

In March 1923 the heart was as enlarged as in 1922; the apical impulse was noted as diffuse and forcible. No murmurs were present. The rhythm was regular. The blood-pressure on admission was 150/60 and on discharge 125/50. She had greatly improved on rest and iodine. The basal metabolic rate was, on admission, +100 per cent. and on discharge +26 per cent. The electrocardiogram was normal in all respects.

In September 1923 she began to have attacks of paroxysmal auricular fibrillation, and during 1924 dyspnoea increased.

In July 1924 the apex-beat was unchanged in position; the electrocardiogram showed auricular fibrillation; the basal metabolic rate was +77 per cent. She was again discharged improved, but was readmitted in November 1924 with a more enlarged heart, the apex-beat being $5\frac{1}{4}$ inches to the left in the sixth space. Auricular fibrillation was present. The blood-pressure averaged 146/75. Marked oedema of the feet, legs, thighs, and abdomen was now present. The basal metabolic rate was +59 per cent. She was given two doses of X-rays (5 H. each time), and on discharge the pulse was regular.

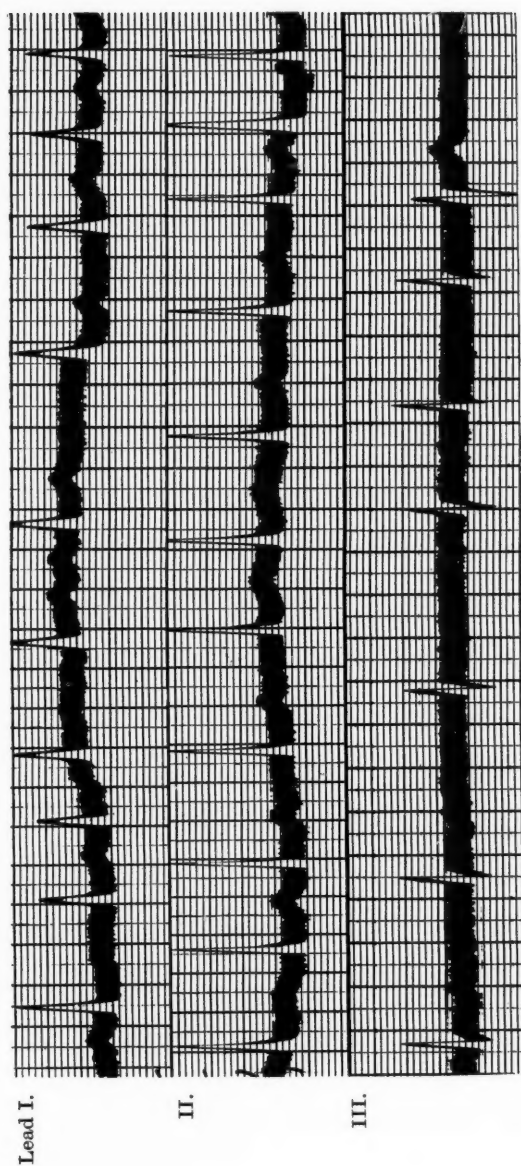


FIG. 4.

She was readmitted in June 1925 with the apex-beat $5\frac{1}{4}$ inches to the left in the fifth space, fibrillating, and with a blood-pressure of 170/90. Oedema of the legs and feet was again present. The basal metabolic rate was +43 per cent. She was discharged improved.

Since that date she has attended the Out-patient Department, being treated with digitalis, to control the ventricular rate, and iodine. Fibrillation has continued.

When seen in 1932 she was in comparatively good health, being able to do her housework and to walk two miles easily. On examination there were no signs of hyperthyroidism; she was of a rather adipose build. The heart was still enlarged, though less so than it had been, the apex-beat being $5\frac{1}{4}$ inches to the left in the fifth space. A localized systolic murmur was audible at the apex. The heart-chest ratio was 0.65, there being a general enlargement of the heart as a whole. The electrocardiogram showed auricular fibrillation, and no left-sided predominance. The blood-pressure was 175/105.

Comment. This patient suffered from the most protracted and severe thyrotoxicity of any of the present series of cases. The heart enlarged during the illness and had remained enlarged since. Simultaneously the blood-pressure had risen progressively. The heart was smaller than it was during the period of active thyrotoxicity. There were few or no signs of failure. Hyperpiesis was now undoubtedly present; it might or might not account for the continued enlargement of the heart. It is the writers' opinion that the heart is larger than pure primary hyperpiesis can account for.

Case 34. S. H., female, aged 51. Was well until August 1923. Exophthalmos then appeared, followed by enlargement of the thyroid, palpitation, and dyspnoea. The symptoms improved temporarily with periods of rest in bed, but on the whole became more severe.

In April 1925, at the age of 44, she was admitted with the classical signs of exophthalmic goitre. The heart was enlarged, the apex-beat being $4\frac{3}{4}$ inches to the left in the sixth space. No murmurs were present. There was auricular fibrillation; slight oedema of the legs was seen. The blood-pressure was 122/76. The tonsils were enlarged and septic. The basal metabolic rate was +45 per cent. She received medical treatment, with iodine, and the tonsils were removed. Quinidine restored the normal rhythm. The electrocardiogram showed no left-sided predominance.

A partial thyroidectomy was performed in July 1925. The section showed the changes of exophthalmic goitre. In November 1925 the basal metabolic rate was +14 per cent.

In March 1932, at the age of 51, she appeared to be well. She had been able to perform busy routine house duties and felt no symptoms. She was a well-covered, rather adipose woman. The heart was enlarged, the apex-beat being 5 inches to the left in the fifth space. No murmurs were audible. Auricular fibrillation was present. The blood-pressure averaged 170/110. The electrocardiogram showed no left-sided predominance. (Fig. 4.)

The X-ray six-foot film showed a heart-chest ratio of 0.67, with a generalized cardiac enlargement.

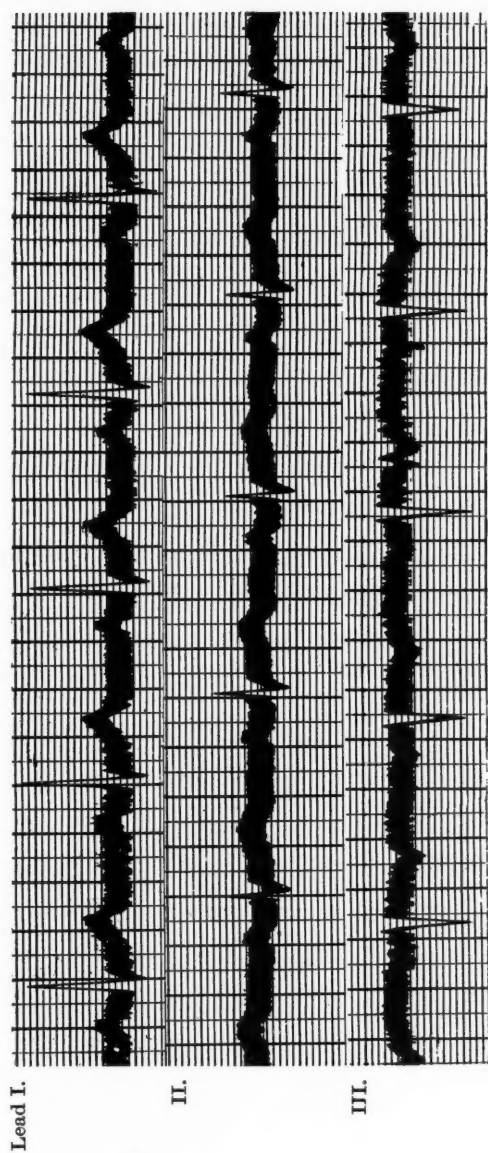


Fig. 5.

Comment. This patient's history did not indicate the presence of any of the known aetiological causes of heart disease. The heart was definitely enlarged during the thyrotoxicosis. The enlargement has persisted. As in the previous case, hyperpiesis has developed since the hyperthyroidism. In the writer's opinion the enlargement is slightly more than could be accounted for solely by the raised blood-pressure. But prolonged auricular fibrillation alone is liable to produce some general enlargement. Taking this factor into consideration together with the hyperpiesis, the enlargement can be explained without postulating a thyrotoxic factor.

Case 35. M. S., female, aged 56. First noticed enlargement of the thyroid in January 1923. Since then the other symptoms of Graves' disease had been present. She was admitted in August 1922, to the surgical ward, aged 46. The cardiac condition was not fully recorded, but auricular fibrillation was present, the tracing showing no left-sided predominance. There was no swelling of the feet.

In September 1924 she was admitted to the medical ward, for palpitation, dyspnoea and oedema of the feet had been noticed. Signs of exophthalmic goitre were still present, and the basal metabolic rate was +40 per cent.

The heart showed some enlargement, the apex-beat being $4\frac{1}{2}$ inches to the left in the sixth space. Auricular fibrillation was present. A soft systolic localized apical murmur was audible. She improved considerably and was transferred to the surgical ward.

In November and December 1924, two further partial thyroidectomies were performed. The sections both showed the changes of exophthalmic goitre. The basal metabolic rate after the first operation was +36 per cent. and after the second +18 per cent. She improved greatly.

In April 1925 the heart was less enlarged, the apex-beat being felt 4 inches to the left in the fifth space. Auricular fibrillation was still present. The blood-pressure was about 125/95.

In May 1925 the normal rhythm was restored with quinidine. The electrocardiogram then showed left-sided predominance. She remained improved, but the ankles occasionally swelled.

In March 1932 she was re-examined at the age of 56. She was suffering from some slight dyspnoea on exertion, but was able to work hard about the house. There were no signs of thyrotoxicosis. She had put on some weight. The heart was somewhat enlarged, the apex-beat being $4\frac{1}{2}$ inches to the left in the fifth space. There was a systolic apical murmur conducted towards the axilla. The blood-pressure was 185/95.

The electrocardiogram showed left-sided predominance, but of the type associated with a transverse heart, as is common in adipose individuals. (Fig. 5.) The X-ray showed a heart-chest ratio of 0.51.

Comment. The radiogram does not show an enlargement out of proportion to that produced by hyperpiesis. The hyperpiesis here, as in previous cases, has arisen after, rather than during, the thyrotoxicosis.

Case 36. A. G., male, aged 33. Came to the Out-patient Department in January 1925. For nine months he had suffered from palpitation, prominence of the eyes, considerable dyspnoea, and some praecordial pain on exertion. The classical signs of Graves' disease were present. The heart was not enlarged and its rhythm was regular.

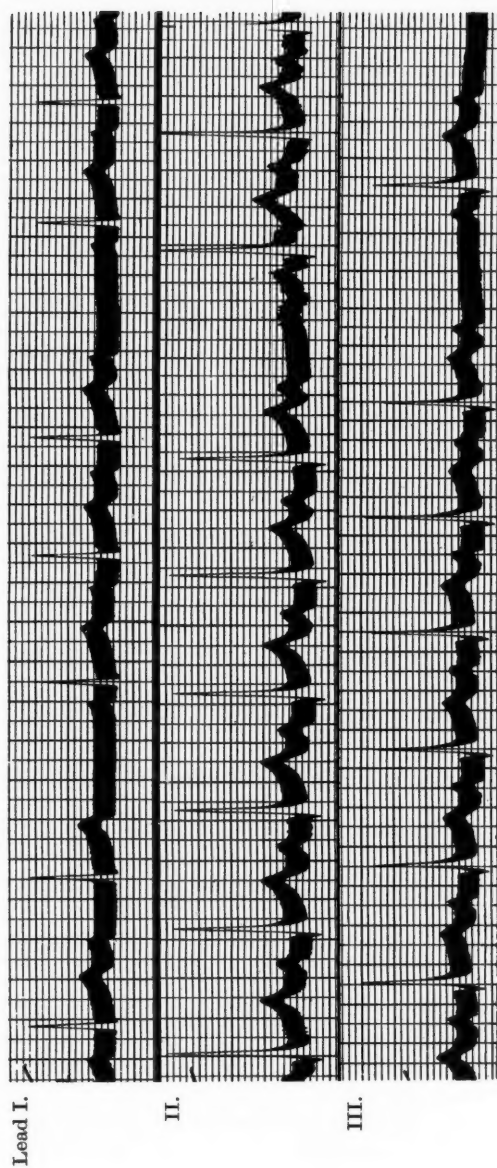


FIG. 6.

In January 1926 he was admitted. The heart was not enlarged; there was no evidence of a valvular lesion. The blood-pressure was 115/68. The basal metabolic rate was +44 per cent.

During his admission a partial heart-block developed. (Fig. 6.) This was completely removable by full doses of atropine sulphate (grm. 1/50). (Fig. 7.)

In March 1926 a partial thyroidectomy was performed. The section showed the changes of exophthalmic goitre, secondary type. After the operation the heart-block disappeared. The electrocardiogram showed no evidence of left-sided predominance.

In February 1927 a second operation was performed. The section showed the changes of exophthalmic goitre. The basal metabolic rate was normal, as was the electrocardiogram.

In March 1932 he was re-examined. He has been leading a normal life with no symptoms of heart failure. The heart was not enlarged, the X-ray showing a heart-chest ratio of 0.48. The electrocardiogram was normal. The blood-pressure was 125/95.

Comment. The presence of a partial heart-block during the hyperthyroidism indicates that at that time there was a cardiac lesion, though other evidence proves that this was not severe. There remains no sign or symptom of cardiac enlargement or disease.

General Conclusions

These twelve cases of myocardial disease following hyperthyroidism are seen to belong to the following groups according to the aetiological factors concerned:

Cases with no discoverable factor other than hyperthyroidism (three cases, 31, 32, and 36, the latter case now showing no enlargement); cases with hyperpiesis (seven cases, 27, 28, 29, 30, 33, 34, and 35); cases with hyperpiesis and rheumatism (two cases, 25 and 26).

The cases with hyperpiesis in whom the cardiac enlargement was slight and in whom the enlargement could be accounted for by that factor alone were three (27, 28, and 35); those in whom an added thyrotoxic factor was probable were four (29, 30, 33, and 34), but in two of these, cases 33 and 34, the presence of prolonged auricular fibrillation complicates the deduction; it is interesting to observe that hyperpiesis was also present in the two rheumatic cases (25 and 26).

Two cases of the whole hyperpietic group are remarkable for the early age at which a raised blood-pressure is seen; case 25 at the age of 25 had a blood-pressure of 160/90, four years after the final partial thyroidectomy; he was of a nervous temperament, but several readings were taken; case 29 had a blood-pressure of 150/100 at the age of 27, seven years after the final operation. This patient was of a calm temperament.

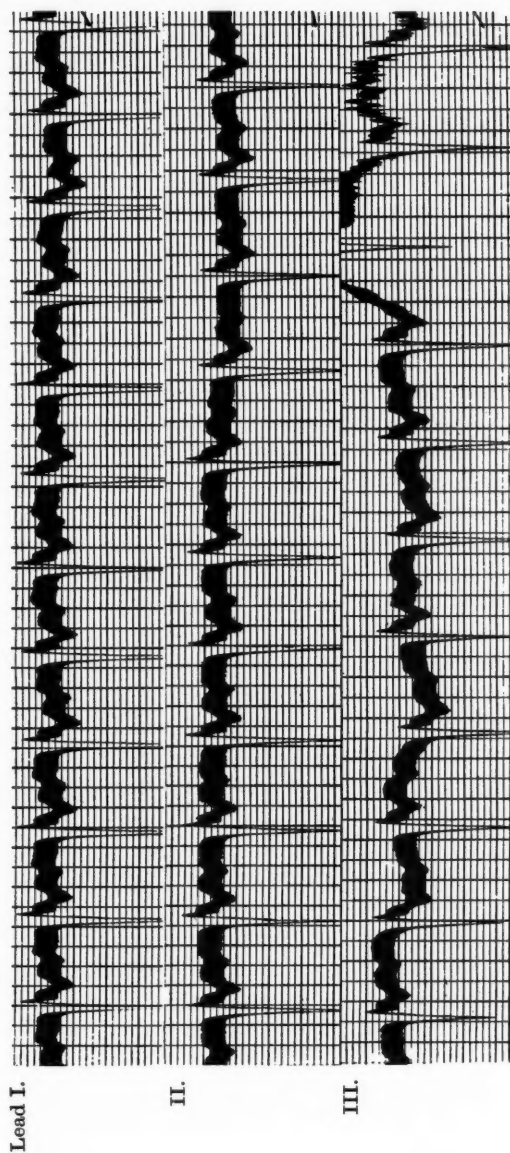


Fig. 7.

Of the two cases with no other discoverable aetiological factor than hyperthyroidism (cases 31 and 32), the following facts emerge.

Case 31, at the age of 27, showed unmistakable evidence of enlargement of the heart, with no evidence of past or present rheumatism. At this age, rheumatism being excluded, the evidence in favour of a thyrotoxic factor is strong. Case 32 presents evidence of a much slighter degree, for the enlargement is slight, and seems to be diminishing. The cause here also is probably the past hyperthyroidism.

In any group of cases with cardiac enlargement a high proportion will present a definite aetiological cause, but when rheumatism, hypertension, syphilis, and chronic pulmonary disease have been eliminated, there will remain a small percentage of cases in whom the cause is not discoverable. Applying this well-known fact to the present group, it is highly probable that in this group of cases of enlargement of the heart after hyperthyroidism there was another causative factor besides the abnormal or excessive thyroid secretion. For it is seen that, of the twelve cases with evidence of myocarditis, two had a rheumatic aetiology, seven had evidence of hyperpiesis, and three of thyroid disease alone. Of the latter group, one had made a complete recovery, a second is recovering, and the remaining case may or may not be an example of hyperthyroidism acting upon a myocardium already implicated in disease due to an undiscovered cause. This suggests that hyperthyroidism will not produce permanent myocardial changes in a heart which is free from the influence of other causes of cardiac enlargement or disease.

The answer to the question, 'Does hyperthyroidism produce any permanent myocardial change under any circumstances?', would seem to be, 'Yes, in patients whose hearts are already subjects of rheumatic or other myocardial change', for some such cases in the present series (29, 30, 33, 34) manifest enlargement of the heart out of proportion to the other causative factor.

In addition to evidence upon this point, a further fact of interest emerged unexpectedly during the investigation, namely, the development of hyperpiesis subsequent to thyrotoxicity.

Of the eleven patients with subsequent myocardial trouble, nine had hyperpiesis following the thyrotoxicity (Cases 25, 26, 27, 28, 29, 30, 33, 34, and 35). In every case there was an interval of time between operative treatment and the final reading. In two cases the readings were not high, but they were *definitely* raised considering the age of the patients; the fact here is, therefore, of considerable aetiological significance (Cases 25 and 27). One case, though at first the reading was within normal limits, showed an increasing systolic pressure (Case 30).

The following table gives in order the number of the case, the former blood-pressure reading, the interval between the elimination of thyrotoxicity, the final blood-pressure reading, and the age at the time of the latter.

Case.	B.-P. 1.	Interval.	B.-P. 2.
25	—	8 years	160/90
26	130/90	1 year	180/100
27	—	1 "	180/100
28	—	2 years	180/110
29	—	7 "	150/100
30	140/100	6 "	160/100
33	125/50	9 "	175/105
34	122/76	7 "	170/110
35	125/95	7 "	185/95

In the case of the two younger patients the hyperpiesis is otherwise unexplained; in the case of the older patients the raised pressure developed subsequent to the hyperthyroidism. That the raised blood-pressure was in each group due to the hyperthyroidism is a reasonable deduction.

Of the patients with normal sized hearts, the following showed some degree of hyperpiesis; the age is given first and the blood-pressure second:

20, 140/90; 43, 180/85; 28, 140/80; 59, 170/90; 50, 175/110. Thus, of a total number of 36, 14 cases show evidence of hyperpiesis.

The mechanism by which hyperthyroidism might be a factor in the production of hyperpiesis is not clear, but the alternatives would seem to be that: the thyrotoxicity might produce permanent and structural changes in the arterioles; the secondary stimulation of the suprarenals might result in a permanent hyperactivity; the prolonged tachycardia might 'wear out' the structure of the blood-vessels more rapidly than would otherwise occur, or that the increased rate of metabolism might accelerate degenerative changes in those individuals in whom such changes would ultimately occur in any event.

If it is fair to argue on the analogy of the results of the investigation of myocardial changes, it would seem reasonable to suppose that just as thyrotoxicity accentuates myocardial change in individuals whose hearts are already the site of myocardial change from some other cause, so in the case of vascular disease hyperthyroidism accelerates the onset of hyperpiesis in those individuals who are predisposed to that condition.

Summary

1. Thirty-six patients who had previously suffered from active thyrotoxicosis, in whom no signs of present thyroïdal activity were discoverable when re-examined for cardiovascular abnormality.

2. Thyrotoxicosis does not produce permanent changes in the normal heart.

3. Thyrotoxicosis may produce an additional myocardial change in hearts affected by some other cause of myocarditis, or predisposed to arteriosclerosis.

4. Thyrotoxicosis may initiate a hyperpiesis, presumably in individuals predisposed to that lesion.

The cases forming the material in this investigation were under the care of Professor F. R. Fraser and of Mr. T. P. Dunhill, who themselves were engaged on a large follow-up investigation on slightly different lines. The authors wish to record their grateful thanks and their sincere appreciation of the generosity which made access to this material possible. They are also indebted to Mr. Geoffrey Keynes of whose histological diagnosis they have made use, and to Miss Vaughan who was responsible for the basal metabolic determinations.

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IDIOPATHIC STEATORRHOEA (GEE'S DISEASE)¹
A NUTRITIONAL DISTURBANCE ASSOCIATED WITH TETANY,
OSTEOMALACIA, AND ANAEMIA

By T. IZOD BENNETT, DONALD HUNTER,
AND JANET M. VAUGHAN

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With Plates 35-43

I. *Definition*

WE have investigated a group of fifteen cases, all of them adolescents or adults, in whom the following main features have been observed: fatty stools with or without diarrhoea, and sometimes with dilatation of the colon, tetany, osteomalacia, anaemia of various types, skin lesions, and frequently infantilism.

All these patients were born in Great Britain and had never resided abroad; with three exceptions they gave evidence that their malady had originated in early childhood. For these reasons, and on account of certain marked differences in the character of the stools in this group, we feel that they cannot be classed with tropical sprue; on the other hand, since the history in the vast majority of cases suggests that these cases began in childhood as typical examples of coeliac disease, there appears to be no justification for the term 'non-tropical sprue' as a description for them.

II. *Historical*

In 1888, Samuel Gee published an account of the 'Coeliac Affection', giving a clear description of a digestive disorder occurring in people of all ages, but especially affecting young children.

He describes in detail the pale, bulky, and offensive stools, notes the occurrence of a similar disease in India, and the rarity of the complaint in adults who had never left England. The absence of obvious aetiological factors is emphasized, together with the negative character of post-mortem examinations in fatal cases; he adds that he cannot tell 'whether atrophy of the glandular crypts of the intestines be ever or always present'.

He describes the extreme emaciation of the body with muscular weakness especially affecting the limbs, together with frequent profound anaemia and a tendency to oedema. He emphasizes distension of the abdomen by gas—

¹ Received August 8, 1932.

'the belly is mostly soft, doughy, and inelastic; sometimes distended and rather tight. Wind may be troublesome and very foetid. Appetite for food differs in different cases, being good, ravenous, or bad.'

He next comments on the protracted course of the disease—'whether the patient live or die, he lingers ill for months or years. Death is a common end and is mostly brought about by some intercurrent disorder.'

In cases which recover there is a grave tendency to relapse, and in children growth is interfered with—even when it tends slowly to recover, they are left frail and stunted'.

Examination of his paper shows that Gee regarded the disease not only as resembling tropical sprue, but as indistinguishable from it, and that although he regarded the coeliac disorder as a disease occurring chiefly in children he was aware of its occurrence in adults even apart from the cases originating in the tropics. Gibbons (1889), writing on the same disease in the following year, states that Gee showed him examples at the Hospital for Sick Children in Great Ormond Street, and it is known that he lectured on the subject at St. Bartholomew's Hospital (personal communication from Sir Archibald Garrod).

Little comment appears to have been excited by Gee's publication, although Cheadle (1903) refers to it in a paper dealing with what he described as 'Achohia'; this paper includes descriptions of five cases of apparent coeliac disease in young children, and one case of tropical sprue. The author believed that these were all due to 'inhibition of the liver'.

In 1902, Bramwell described the case of an adolescent with infantilism and fatty stools but no sign of rickets; this patient was followed and described, particularly with regard to the effects of treatment by pancreatic extracts, in subsequent communications, and other similar cases were collected by the same observer. In his later publications Bramwell noted swelling and tympanites of the abdomen, non-union of epiphyses, anaemia, and in one case tetany and achlorhydria, but he claimed to have achieved complete arrest of symptoms and cure of infantilism by the administration of pancreatic extracts. The cases of Thomson (1904) and Rentoul (1904) are quoted by him in support of his thesis that these cases should be regarded as 'pancreatic infantilism'. Bramwell's conclusion as to the pathology of the condition is based chiefly on the result of Sahli's test and is not supported by post-mortem evidence.

In 1908, Herter rediscovered the disease and published a short book, *Infantilism and Chronic Intestinal Infection*. Herter's book is based on five cases in children together with five others of shorter duration which he had studied in collaboration with Holt. The points stressed by him are: (1) Arrest in the development of the body. (2) Maintenance of mental powers and fair development of the brain. (3) Marked abdominal distension. (4) Anaemia of moderate degree. (5) Rapid onset of physical and mental fatigue. (6) Various obtrusive irregularities referable to the intestinal tract.

Concerning the pathogenesis of the condition he emphasizes—and indeed this represents the main thesis of his work—intestinal infection as the cause of the disease. This aspect of Herter's publication must be considered as a defect, for subsequent work has not confirmed his view of the importance of his bacteriological findings in the disease.

Herter comments on the occasional occurrence of rickets and on the changes sometimes observed in the tongue: 'in four or five cases of infantilism there were very slight indications, but it may be said in general that the signs of rickets, if present at all, do not form part of the symptom-complex at present under discussion. Outside the present group I have seen well-marked instances which showed no signs of rickets.'

Later on he says: 'the tongue is apt to be somewhat more red and the papillae swollen, but in none of these cases was there any denudation of epithelium or any indication of the occurrence of geographical tongue. The tongue is at times slightly swollen and on its edges marked by impressions of the teeth.'

The most notable addition by Herter to our knowledge of the disease is contained in the metabolic studies given by him. He showed by a series of well-conducted experiments that there is practically no positive calcium balance in these cases. Further, he gave full chemical analyses of the faeces showing 30 to 40 per cent. of fat in the stools both as total fat and as soaps. He showed that the greater part of the fats lost was in the form of fatty acids, and that the sum of the fatty acids and the soaps made up on the average about three-quarters of the total fat lost.

'These losses cannot of course be attributed to any failure of fat-splitting in the intestine, but are clearly referable to a diminished power of absorption.' He stressed the effect of this in preventing calcium and magnesium absorption. 'It is true that only a relatively small percentage (say 10 per cent.) of the calcium lost in the faeces is present in the form of soaps, but it is obvious that the non-absorption of the quantity of calcium represented by this proportion is enough to determine whether the organism shall or shall not gain calcium for the purpose of building up the skeleton.'

In his description of the causes of the retardation of development in these patients he says that it depends on a simple cause, namely, insufficiency of the foodstuffs absorbed from the digestive tract:

'Metabolic derangements do to some extent exist, but they are to be considered as secondary to the absorption of mildly toxic but continually formed products.'

He points out the intolerance for carbohydrates present in such patients, and this he considers to be less important than the intolerance for fat because the former does not bring on symptoms. Protein absorption he found to be much better, in spite of the fact that it was somewhat impaired. The failure of calcium absorption he emphasized as being due to calcium loss in the stools, and he stressed the rapid decomposition of dextrose by bacteria.

In 1909, Heubner published an account, largely inspired by Herter's

book, of the same disease, which attracted sufficient attention in Germany for the condition to be referred to frequently under his name in later publications. Indeed the whole of the literature on this subject tends to be rendered ambiguous through the condition being described sometimes as Gee-Herter disease, sometimes as Herter-Heubner disease, sometimes as coeliac disease, and occasionally as non-tropical sprue.

During the second and third decades of the present century medical literature has contained, with increasing frequency, references to the condition first described by Gee. Articles are to be found under a variety of headings, for the disease may be characterized by many striking symptoms, any one or any number of which may focus the attention of an individual observer. According to which of the several features of the disease has appealed to an observer we find references in the literature particularly under the following headings:

1. Coeliac disease as a diarrhoeal disease affecting the growth in children. The work of Parsons and of Reginald Miller in this country is of particular importance in this respect.

2. Resemblances of the condition to tropical sprue have created interest in a different group of observers, amongst whom Thaysen may be quoted as the principal. The recent observations of Holmes and Starr on a nutritional disturbance in adults, resembling coeliac disease and sprue, fall into this group.

3. The association of tetany with steatorrhoea has led to an abundant literature, one of the earliest and most complete examples of which is the article by Langmead (1911).

4. Coeliac disease as a cause of rickets has been particularly studied by Parsons, Hess, and Schaap.

5. The haematological features of the disease have been reviewed by Fanconi (1928), Strandqvist (1929), and Thaysen (1931).

6. The obscurity of the metabolism in coeliac disease has excited considerable attention amongst biochemists; the work of Schaap, of Linder and Harris, and of Macrae and Morris, may be cited as examples.

A survey of this literature as a whole makes it apparent that the condition described by Gee forty-four years ago is not a disease confined to childhood alone, but that it may become conspicuous during adolescence or may call for attention in adult life, and even in old age. It is further notable that in addition to emaciation, fatty diarrhoea, and infantilism, there are many other striking manifestations, of which tetany, rickets, osteomalacia, anaemias of various types, and megacolon, are the most conspicuous, but few writers have attempted a complete survey of the subject. The fullest descriptions are to be found in the articles of Fanconi, of Lehndorff and Mautner, of Schaap, and of Thaysen. In the English language no such survey has hitherto been attempted.

III. *General Manifestations*

As already stated, all cases in the present series occurred in adults or adolescents. This possibly renders the symptomatology of the group different from that usually considered as typical of coeliac disease, which is generally regarded as a disease of children.

TABLE I
Relationship of Age of Patient and Nature of Presenting Symptom

Case.	Age of onset of first symptoms.	Nature of first symptoms.	Present age.	Presenting symptom when seen by authors.	Present condition.	Work.
1	11 yrs.	Legs bent. General weakness	16 yrs.	Genu valgum	Invalid	—
2	Infancy	Rickets	26 yrs.	Genu valgum	Invalid	Work in factory 14-18
3	1 yr.	Diarrhoea	17 yrs.	Bony deformities	Invalid	—
4	3½ yrs.	Diarrhoea, cessation of growth	15 yrs.	Genu valgum	Semi-invalid	—
5	16 mos.	Rickets	58 yrs.	Deformities. Diarrhoea	Invalid	—
6	Infancy	Diarrhoea	34 yrs.	Diarrhoea	—	Watchmaker
7	Infancy	Diarrhoea	22 yrs.	Tetany and diarrhoea	—	Student of music
8	Infancy	Diarrhoea	40 yrs.	Diarrhoea and tetany	Invalid, v. little housework	—
9	13 mos.	Bony deformity. Occasional diarrhoea	34 yrs.	Diarrhoea and tetany	Invalid	—
10	10 yrs.	Not growing properly. Diarrhoea	19 yrs.	Infantilism. Diarrhoea	—	Inspecting parts at aero-plane factory
11	Infancy	'Consumptive bowels'	35 yrs.	Tetany. Diarrhoea	—	Inspecting parts at rubber factory
12	52 yrs.	Diarrhoea	57 yrs.	Tetany. Bone pains	Invalid	—
13	18 mos.	'Consumptive bowels'	19 yrs.	General weakness	—	Garage hand
14	Infancy	Diarrhoea	16 yrs.	Bone deformities	Invalid	—
15	13 yrs.	Knock-knee	56 yrs.	Weakness. Diarrhoea	Dead	Clerk

Steatorrhoea and disturbances of calcium and phosphorus metabolism alone were constant findings in all cases. Bone deformities or bone pains were the presenting symptoms in seven cases (Table I), diarrhoea in eight cases; five cases complained of tetany. Inquiry into past history showed that twelve cases gave diarrhoea as the earliest symptom and six

bone deformity. Except in one instance, anaemia was only found on investigation. The wasting and distended abdomen so constantly described in children was not a noticeable feature in most cases, even though severe diarrhoea was present.

Age. Though all cases in the present series occurred either in adolescents or adults (Plate 35, Fig. 1) it proved possible, in the majority, to elicit either from the patient or parents a history of 'rickets' or 'consumption of the bowels' in infancy. There was later an apparent latent period during which symptoms were in abeyance in some instances. Case 11 had worn napkins until the age of seven, but was thirty-five years of age when he first presented himself at hospital with symptoms which led to a recognition of the condition.

Eleven cases gave a history dating from infancy; in three others significant symptoms were present before the age of thirteen years. In only one instance therefore (Case 12) was there no history until the onset of diarrhoea at fifty-two years of age.

Parsons (1931) in discussing the age incidence of coeliac disease states that the 'onset is usually insidious during the age period of nine months to two years'.

The suggestive history is sometimes only obtained after careful questioning, which probably accounts for many of the apparently spontaneous cases occurring in adults which have been reported by Blumgart (1923) and Holmes and Starr (1929).

Tileston and Underhill (1923), Findlay and Sharpe (1920), Constam and Partch (1929), Linder and Harris (1930), Poynton, Armstrong, and Nabarro (1914), record adult cases with a history from childhood. It is reasonable, therefore, to conclude that idiopathic steatorrhoea associated with tetany, anaemia, and osteomalacia is *par excellence* a disease originating in childhood, though not necessarily recognized until adolescence or adult life is reached.

Sex. In the present series eight cases occurred in women, seven in men. Schaap (1926) analysing the literature in 1926 found thirty-three cases of coeliac disease in males and thirty-nine in females. Parsons (1931) likewise concludes that it is more common in females.

Nationality. The present cases were all of British extraction, and, so far as could be ascertained, had no continental forebears, a point of some importance in Cases 2 and 6.

Idiopathic steatorrhoea or coeliac disease has been described in the Scandinavian countries, Germany, Switzerland, France, Great Britain, and America. There are no recorded cases occurring in children of Indian or Negro stock.

Family history. There is no evidence either in the literature or in the present series to suggest that the disease is either familial or congenital. In no instance has it been possible to obtain a significant family history.

Physical disability. Nine cases in the present series remained complete or

semi-invalids in spite of treatment which had improved, though not cured, their condition (Table I). Case 12 had been well and led a normal life until the age of fifty-two, but now can only get about with difficulty. Case 2 had worked for four years on first leaving school, but now is crippled. Cases 4 and 8 had never been able to do more than light housework. None of the six cases at work was capable of hard manual labour, while the four adult cases had frequently been interrupted in their occupations by serious illness. Bone deformities, associated with general weakness, were the outstanding cause of permanent disability. Tetany and diarrhoea, found on examination to be often associated with anaemia, were the most frequent presenting symptoms, which could, however, be relieved by treatment.

External appearances. Poynton, Armstrong, and Nabarro (1914), in their study of coeliac disease in children, state that 'when the condition has existed for some years there is a decided resemblance in the appearance of these children . . . one extreme case in adult life at the age of twenty-four seemed like a girl of sixteen years'. This typical appearance was as remarkable in the present group of adult patients, especially in those in whom the history dated from infancy (Plate 35, Fig. 2).

The infantilism, deformity of the skeleton and distended abdomen are described elsewhere, but there are other common characteristics.

1. *Primary sex characteristics.* In two men the genitalia were infantile, and they were poorly developed in a third. In the women menstruation either had not occurred or else was delayed in onset, with three exceptions who gave a normal history. Two of the latter had had one child and the third had miscarried at three and a half months.

2. *Secondary sex characteristics.* In long-standing cases secondary sex characteristics are frequently either absent or poorly developed, accentuating the childish appearance of the patient (Plate 35, Fig. 2). Thus in four out of the seven males discussed the voice was still high-pitched, and in two the distribution of hair was infantile.

3. *Anaemia.* In his original description of coeliac disease, Gee states that 'cachexia, a fault of sanguification betokened by pallor and a tendency to dropsy, is a constant symptom'. The clinical appearance of the patient is dependent upon the type of anaemia present. Patients with megalocytic hyperchromic anaemia have the malar flush and slight yellowing of the conjunctivae so typical of Addisonian pernicious anaemia. Those with a hypochromic anaemia on the other hand show a dirty putty-coloured pallor with bluish-white sclerotics which is characteristic of this type of blood deficiency. With one exception the patients in both groups showed the fine mud-coloured hair which is liable to turn grey in the early twenties so often found in severe anaemias of all types. One patient (Case 10) had extremely defective growth of hair on the scalp and always wore a wig (Plate 36, Fig. 3).

4. *Skin.* The frequent occurrence of skin lesions in the present series appears too striking to be mere coincidence. They were noted in seven cases and described by the dermatologists as psoriasis, eczematous or pustular

dermatitis. Sometimes small abraded erythematous areas occurred on the dorsal aspects of the limbs and occasionally on the body. In Case 13 there was a patch of pellagra-like pigmented eruption over the left ankle. Case 2 showed a red erythematous eruption with a bat-wing distribution on the face. In one instance, Case 8, the skin condition was so severe as to be the presenting symptom on admission to hospital. There were large, moist, red, abraded areas, from 2 cm. to 8 cm. diameter, on all limbs and to a lesser extent on the trunk. Many of these lesions showed scaly-brown pigmented borders; one on the calf had a deep-brown scaly periphery and a moist, red, abraded centre, the whole appearance being not unlike pellagra (Plate 36, Fig. 4). The condition cleared up within three weeks when the patient was given large doses of marmite on account of her severe megalocytic anaemia. The improvement in the skin condition, which was as striking as that in the blood, was probably due to the rich Vitamin B content of the marmite.

Constam and Partch (1929) have described a somewhat similar case in a woman of thirty-four. Associated with tetany and osteomalacia she had a skin lesion consisting of symmetrical, dry red areas which had appeared in the region of the wrists, elbows, knees, neck, shoulders, groins, and external genitalia and was diagnosed as pellagra. The lesions disappeared when the patient was given a high vitamin diet. No examination of the fat content of the stools was made, but the authors conclude that the whole syndrome was probably due to a nutritional disturbance. Thaysen comments on the frequency of pigmentation, but does not describe any specific skin affection, nor does Fanconi. Presumably the skin lesions, like others of the syndrome, are due to a deficiency brought about by defective intestinal function.

5. *Clubbing.* Fanconi noted the clubbing of the fingers in some of his young children. Clubbing of the parrot-bill type was present in six of the present cases, affecting the toes as well as the fingers in some instances, while in five cases the finger and toe nails showed a typical antero-posterior curvature (Plate 36, Fig. 5). In a sixth case, during the acute phase, the finger nails were soft and easily broken, but improved with treatment of the general condition.

6. *Teeth.* It appears at present impossible to draw any conclusions as to the teeth. Parsons (1931) considers that as a rule dentition is delayed and that in some cases the enamel is badly formed. In five cases in the present series they appeared good or only showed slight caries. Three patients stated that the teeth decayed rapidly, and in Case 5 they had all been lost at the age of twenty. In three other cases all teeth had been removed either for decay or sepsis. Such changes had no relationship to the length of history or to the severity of the other symptoms. In three instances, when special examinations were made, the teeth were reported 'certainly not to be hypocalcified but, if anything, hypercalcified, i.e. more translucent than normal for the age'.

7. *Lens changes.* Changes in ectodermal tissues are, of course, well known in tetany. They consist of cataract, brittleness and ridging of the nails, loss

TABLE II

Infantilism and Changes in the Bones

Case No.	Age.	Sex.	Infantilism.	Bone deformities.
1	16	M	+	Genu valgum sufficient to prevent walking relieved by osteotomies after admission. Bossed wrists. Beaded ribs. General osteoporosis. Rickets of metaphyses
2	26	M	+	Genu valgum. Fracture of clavicle. Bossed wrists. Beaded ribs. Osteotomy. Bending of tibia and brim of pelvis. Skull normal thickness. Considerable osteoporosis. Delayed union of epiphyses
3	17	F	+	Extreme bending of femora, tibiae, and fibulae; legs had been straightened by osteotomies several years previously but had re-bent. Several fractures in recent years. Patient has walked but has never run. Bossed wrists. Beaded ribs. Splayed thorax. Broke femur at 18, and opposite femur at 19. General osteoporosis. Delayed union of epiphyses
4	15	F	+	Genu valgum. Bossed wrists. Beaded ribs. Osteotomy. Definite osteoporosis. Rickets of metaphyses. Delayed union of epiphyses
5	58	F	+	Marked genu valgum. Great deformity with beaking of pelvis. Marked thickening of calvaria with parietal bossing. Bowing of forearms, femora, and tibiae. Deformity of ribs. Diffuse osteoporosis
6	34	M	+	Bowing of femora. Genu varum. Marked thickening of calvaria with frontal and parietal bossing. Prominent malar bones. Beaded ribs. Harrison's sulci. 'Arm' broken at 9 months. Definite osteoporosis. Delayed union of epiphyses
7	22	F	Nil	No bone deformity. No history of fracture. Slight generalized osteoporosis. No rickets of metaphyses. Epiphyseal union normal
8	40	F	Nil	Occasional pain in bones. No history of fracture. No abnormality in radiograms of bones
9	34	F	+	Severe genu valgum sufficient to prevent running. General osteoporosis. Bending of tibiae. Gross deformity with beaking of pelvis. Union of epiphyses normal
10	19	F	+	Dwarfism. No other abnormality in bones
11	35	M	Nil	Genu varum. Slight bowing of tibiae. No fractures. No osteoporosis
12	57	F	Nil	Walks with difficulty, bent and limping. Bones tender, especially those of thorax. Slight scoliosis. Gross pelvic deformity. Fractures of pubis, one rib, and ulna. Considerable osteoporosis with thin trabeculated corticales
13	19	M	+	Genu valgum. Bossed skull. Beaded ribs. Splayed costal margins. Pelvis slightly deformed. Healing fractures of right tibia, left tibia and fibula, right ulna. Great osteoporosis with trabeculated corticales of long bones. Skull normal in thickness but finely mottled. No rickets of metaphyses. Great delay in union of epiphyses
14	16	M	+	Can stand with support but is unable to walk. Severe genu valgum. Gross bossing of wrists and beading of ribs. Splayed costal margins. Bowed forearms. Scoliosis. Triradiate pelvis. Old fracture of right clavicle. Recent fractures of three ribs. Great osteoporosis with extensive rickets of metaphyses. Skull normal thickness. Great delay in union of epiphyses
15	56	M	Nil	Great outward and slight anterior bowing of femora in spite of osteotomies years before. Left tibia bowed. Slight osteoporosis. Epiphyses normal

of hair, and defects in the enamel of teeth giving rise to several transverse ridges one above the other. None of these changes is common, but the first is met four times as frequently as any of the other three. The association of cataract with tetany was first recorded about fifty years ago. It has been described in endemic tetany, post-operative tetany, rickets, spontaneous hypoparathyroidism, and idiopathic steatorrhoea (Hunter, 1930). Lenticular opacities have not yet been reported in young children with coeliac disease (Parsons, 1932). Since 1924 it has been possible by means of the slit-lamp to demonstrate opacities in the lens where no visual disturbance exists. In our fifteen cases thirteen were examined by this method, and of these six showed opacities and seven showed none. In no case did the opacity interfere with vision. The slit-lamp appearances resembled those of post-operative tetany. There were small flaky and powdery opacities in the various layers of the lens (Plate 41, Fig. 15). Less commonly, small crystalline opacities, sometimes coloured, were seen. We can offer no explanation for this phenomenon beyond the fact that the serum calcium in all our cases was low as it is in post-operative tetany. It would seem irrational to postulate hypo-parathyroidism on a mere physical resemblance of changes in the lens. Since the patients showing these opacities varied in age from sixteen to forty years, it seems reasonable to suppose that the risk of blindness from cataract is even less than is the case with post-operative tetany.

The Wassermann reaction. The Wassermann reaction was negative in all cases in the present series. There is no evidence in the literature to suggest that the condition is in any way associated with a syphilitic infection.

IV. *Skeletal System*

Stunting of growth and infantilism have been noted by many writers on coeliac disease. The occurrence of bone deformities, however, seems to have escaped recognition until recently. In 1912 McCrudden and Fales described a case of coeliac disease in a boy aged ten years where the bones showed osteoporosis and fractures. Parsons (1913) stated that rickets was not an uncommon complication of coeliac disease. Miller (1920) described a case showing definite rachitic changes, and added the comment 'in this disease in which the absorption of fat is so conspicuously defective, it is curious that changes in the long bones are so much less frequent than in renal infantilism'. Lichtenstein (1921) denied that there was any connexion between rickets and coeliac disease, but nevertheless found that out of a total of nine cases two showed slight and three severe rickets. Lehmann (1925) discusses the relation of coeliac disease to rickets, and states that rickets occurs in all cases some time or other in the development of the disease. It is constant in advanced stages of the disease. In one of his cases at the age of six there was no X-ray sign of bone disease, whereas eighteen months later florid rickets was demonstrated, the explanation being that the patient began to

grow rapidly at just this age, namely seven and a half. Lehnndorff and Mautner (1927) state that the absence of rickets may be striking; patients rarely complain of spontaneous pain in the bones, but pain on pressure is occasionally observed; infraction or even fracture on very slight trauma is not uncommon. They mention that a child may fracture the femur sliding on the floor, or the radius falling on the outstretched hand. They describe the following characteristics of the radiograms of bones. They are poor in calcium, pathologically transparent, the spongiosa is wide-meshed, the bone spicules thin and few, and the corticalis thin and sharply demarcated. Parsons (1927) shows that bone changes are of frequent occurrence in severe cases of coeliac disease, provided that the disease be of long standing. He finds in not a few cases deformity of moderate degree—rarely there are very severe deformities with multiple fractures. His evidence that the bone changes are rachitic in origin is complete. It comprises the clinical characters, low blood phosphorus, sometimes low blood calcium, characteristic radiograms, and the fact that the changes can be cured or prevented by the administration of vitamin D. Thaysen (1931) points out that in young children with coeliac disease growth is so much delayed that florid rickets does not appear: all that is found is osteoporosis.

The occurrence of bone changes in the idiopathic steatorrhea of adult life was first recorded by Holst (1927). He described a case of 'non-tropical sprue' in a woman of 33, who showed kypho-scoliosis and multiple spontaneous fractures of the ribs. The patient had never left Denmark; her illness dated back to rickets in childhood. For five years she had suffered from periodic attacks of diarrhoea with nausea and vomiting. Later she became weak, lost so much weight that she was thought to suffer from progressive muscular atrophy, and had severe attacks of tetany. The abdomen was greatly swollen, the Chvostek and Trousseau signs positive, and prominences were found on the seventh, eighth, and ninth ribs near their angles. There was a megalocytic hyperchromic anaemia, free hydrochloric acid was found in the test meal, and the sugar tolerance curve was low. The faeces contained a large excess of split fats. She died of haemorrhage into the jejunum, but unfortunately no statement is made about the bones in the autopsy report. This author states that the abnormal fragility of the bones is evidently due to a great loss of calcium in the stools as calcium soaps. He points out that this is a cause of decalcification of the bones and spontaneous fractures which he has not seen described elsewhere.

In 1929 Holmes and Starr investigated a nutritional disturbance in adults resembling coeliac disease and sprue and characterized by emaciation, anaemia, tetany, chronic diarrhoea, and malabsorption of fat. One of their cases, a woman of 53, complained of pains in the larger joints. Controlled radiograms showed a very marked decrease in bone density, but gave no evidence of arthritis.

The case of pellagra associated with osteomalacia and tetany reported by Constam and Partch (1929) was probably one of idiopathic steatorrhea.

The patient was a nun aged 34 who had lived in Missouri all her life. Since childhood she had suffered almost every summer from an attack of diarrhoea lasting about three weeks. For six years she had complained of pains in the lumbar spine, pelvis, and right lower thorax. Walking became more difficult, and ultimately she had been obliged to use crutches. Tetany appeared and was at times coincident with the attacks of diarrhoea. There was marked kypho-scoliosis and the sternum and lower ribs were tender to pressure. Radiograms of the bones revealed a marked degree of osteoporosis, but no sign of fracture was found.

Linder and Harris (1930) described the case of a woman of 33. She was quite disabled by tetany and bone pains, and examination showed a well-marked dorsal kyphosis with widespread tenderness in the spine, lower ribs, and crests of the iliac bones. Radiograms showed very poor shadows of the bones examined, and many fractured ribs. These authors discuss the possibility that the changes in the bones were those of osteomalacia. This view is justified by the fact that on treatment with irradiated ergosterol 'improvement in the patient very slowly became apparent; the great tenderness disappeared, walking ceased to be a torture, and some increase in density of the bones was apparent'.

Thaysen (1931) emphasizes the occurrence in 'non-tropical sprue' of bone pains in the neighbourhood of the great joints. He points out that the pain and tenderness in the lumbar region and pelvis, the diminished height, and the laborious cautious gait, are symptoms comparable to those found in hunger osteomalacia during the war of 1914-18. He records relief of such pains in two of his cases of non-tropical sprue treated by means of ultra-violet irradiation. In his discussion of this point he claims that since the osteoporosis disappears on treatment with irradiated ergosterol it follows that it must have been due to lack of vitamin D.

In our series of fifteen cases we met no instance of a normal skeleton (Table II). Ten cases were dwarfed, but the infantilism of stature was not necessarily associated with mental or sexual infantilism. Where the bone changes were of great severity and dated back to early childhood the patient had often been deprived of instruction, but was nevertheless intelligent (Case 14). Sometimes the physical disability had encouraged studious habits in an intelligent individual, who then became well-read and in other ways well informed (Case 9). The dwarfism was in one case associated with failure of development of primary and secondary sex characters without impairment of intelligence (Case 10).

Turning to the deformities of the skeleton apart from dwarfism we find that only two cases in our series of fifteen escaped, and even in these two the skeleton was not normal, for one had pain and tenderness in the bones, and the other had osteoporosis, as demonstrated by radiograms. One case was dwarfed but not otherwise deformed (Case 10). In the twelve remaining cases, whether dwarfism was present or not, the bones were in some way deformed. For example, only one of the twelve individuals had straight

knees; of the eleven remaining eight had genu valgum and three genu varum. In the great majority of cases the bone deformity dated back to childhood. Bending and bowing of the bones was in two cases so severe that the patients could not walk and were unable to stand unaided (Plate 37, Fig. 6). Osteotomies, usually on the femora, had been performed in four cases. Six patients gave a history of fracture or showed during investigation one or more spontaneous fractures of bone. The spontaneous type of fracture was usually not disabling. It occurred without displacement and gave rise to localized pain and tenderness.

Beading of the ribs was found in six cases (Plate 37, Fig. 7), and bossing of the wrists and ankles in four (Plate 37, Fig. 8). The subcostal margins were splayed out to a marked degree in four cases. This deformity is, of course, associated with the abdominal distension with or without megacolon.

Radiograms showed distortion of the pelvis in five cases. Sometimes this was merely a flattening of the brim of the pelvis opposite the acetabulum; more often it was a gross deformity giving rise to a triradiate or beak-shaped brim (Plate 38, Figs. 9 and 10). Except in Cases 5 and 6 radiograms of the skull showed no abnormal thickness of the calvaria. This is rather surprising, considering that frontal and parietal bossing were often encountered on physical examination. Thickening of the malar bones, associated with a mongoloid appearance of the face, was seen in Case 6 (Plate 39, Figs. 11 A and 11 B), and to a less extent in Case 2. This change is probably due to alterations in the bony structure of the superior maxillae and malar bones. As such it does not lend itself readily to demonstration by radiography. The condition resembles that described by Cooley (1927). It is impossible, however, to identify his cases with ours since in none of his was steatorrhoea recorded.

Controlled radiograms showed osteoporosis of varying degrees in twelve of our cases. In only four of these was it possible to demonstrate the translucent cup-like metaphyses of rickets. Sometimes striking osteoporosis would be found with no rickets of the metaphyses (Case 13), and here it must be assumed that the arrest of growth prevents the appearance of florid rickets. Severe rickety changes were by no means absent in our cases (Plate 40, Fig. 12); for example, a boy of 16 (Case 14), evidently growing more rapidly than a boy of 19 (Case 13), showed extensive pale cup-like metaphyses in addition to striking osteoporosis. Many cases showed transverse lines of increased density adjacent to epiphyses. If these lines are indeed associated with cessation of growth, there is every reason in this disease for the appearance of large numbers of them. In one case the metaphysis of a long bone showed seven closely set, parallel, transverse lines.

The details of the osteoporosis could readily be picked out in contrast to the controls. Thinning and coarse trabeculation of the corticales of long bones are pronounced in severe cases (Plate 41, Fig. 14). In mild cases the ivory corticalis was too thin, and insufficiently dense. Osteoporosis of the spongiosa consisted not only of faintness of the bone shadows but also of an increase in the width of the mesh. Failure of epiphyses to unite was found

in seven of the ten cases showing infantile characteristics. Where infantilism was severe the failure of closure of the epiphyses of the small bones of the hand was seen in sharp contrast to the control (Plate 40, Fig. 13).

The only original observation we have to offer concerning the bone disease in these patients is the histological proof of osteomalacia in three cases. In one of these, a man of 56 (Case 15), a summary of the necropsy report and a detailed description of the skeleton is given by Professor H. M. Turnbull (p. 675). It is proposed to publish the complete report of this case elsewhere. In Case 12, a woman of 57, a piece of bone was removed from the right tibia for purposes of diagnosis. The histological findings are set out in detail by Professor Turnbull on p. 669. In Case 2, a man of 26, a portion of bone removed by osteotomy from the lower end of the femur was examined histologically and is reported upon by Professor S. L. Baker on p. 652. In a fourth case Professor Baker was unable to find histological evidence of osteomalacia in a portion of bone removed at operation. This was a boy of 16 (Case 1). Double osteotomy of the lower ends of the femora was performed for genu valgum.

V. *Gastro-Intestinal Phenomena*

(a) *The tongue.* In five of our fifteen cases there were changes in the epithelium of the tongue (Table V). A history of 'sore mouth' in childhood was sometimes elicited on questioning the parents of the patient, but the patients themselves seldom complained of any such symptom. On examining them it was discovered, particularly in Cases 2 and 6, that the tongue presented the bald and shiny appearance due to atrophy of the filiform papillae so frequently associated in clinical medicine with anaemias of various types.

Such changes in the tongue have been described by Herter (1908), Still (1918), Cautley (1921), Holmes and Starr (1929), and Marble and Bauer (1931). In contrast to the almost constant occurrence of sore mouth in tropical sprue it must be noted that in the condition we are describing this symptom is an occasional rather than a frequent occurrence, although Thaysen (1929) found various degrees of glossitis in 23 out of 30 patients with 'non-tropical sprue'. It is clearly, therefore, sufficiently common to be more than an accidental happening. It must, on the other hand, be noted that no constant relationship exists between this glossitis and achlorhydria. Table V shows the actual findings in our series.

(b) *Gastric symptoms,* in the form of vomiting and post-prandial indigestion, were described by a few of our patients as forming part of their past history; they were not seen whilst they were under our personal observation. Fractional gastric analysis revealed complete achlorhydria with low total acidity in two out of twelve cases examined (Table V). Certain writers, notably Lehndorff and Mautner (1927), Levinsohn (1927), Marriott, Davidson and Harshman (1922), have held that achlorhydria or achylia gastrica is a practically constant finding in coeliac disease; it is impossible to substantiate this theory, although in certain limited series of observations it may,

by coincidence, have been constant; thus Taylor (1922) found achlorhydria in each of five cases examined, but it is to be noted that in two of that series free hydrochloric acid returned at a later stage in treatment. Similarly Holmes and Starr (1929) in their series found one case with achlorhydria whilst three showed normal secretion. Achlorhydria was present in each of Blumgart's (1923) two cases, and was present in the case reported by Snell and Habine (1927). Fairley (1930), in a study of the gastric secretion of tropical sprue, finds that complete achlorhydria was present in fourteen out of a total of forty-four collected cases; in eleven others the secretion of hydrochloric acid was greatly reduced. It would therefore appear that achlorhydria is a somewhat frequent, but by no means constant, accompaniment of this disease, and occurs in a percentage of cases somewhat similar to its incidence in tropical sprue. Our observations on this point coincide with those of Fanconi (1928) and of Thaysen (1931).

(c) *Abdominal distension* was a conspicuous feature in certain cases, but was not present in every instance. The past history in several instances revealed that during some period of childhood a diagnosis of tuberculous peritonitis had been made. Gee (1888), in his original description of the disease, refers to the frequency with which such patients describe their condition as 'consumption of the bowels', and it is of interest to note that this phrase is still employed by patients to-day; it also indicates the difficulty of diagnosing this condition from tuberculous peritonitis. In a later paragraph we deal with the relative infrequency of actual diarrhoea in the adolescent and adult cases which are here studied. It is natural that when this symptom is less prominent abdominal distension should also be diminished. With the patient in the erect attitude, protuberance of the abdomen is conspicuous, and in the prone position, even if diarrhoea is absent, the flabby, atonic abdominal wall, tendency to eversion of the umbilicus, and somewhat doughy resistance to palpation, usually form a striking picture. When the abdominal wall is not very wasted it is difficult to be certain that free fluid is not present, but usually the patient is sufficiently thin for it to be possible to demonstrate that the distension is entirely gaseous.

The distension may be chiefly in the small intestine or confined to the colon; during acute exacerbations it is chiefly in the former. Pain is seldom conspicuous, but during periods of diarrhoea may become sufficient to attract attention.

(d) *Dilatation of the colon.* Whenever possible our cases were examined for dilatation of the colon by means of X-ray examination after the administration of barium enemata. In six out of eight cases examined the colon was abnormal, dilatation being present from a moderate degree affecting the descending colon only, to an extreme dilatation of the whole of the large bowel, sufficient to justify the use of the term 'megacolon'. This was seen particularly in Case 3 and Case 8, where the colon was so large that bulging of the lower thorax was produced, and the normal liver dullness

almost completely abolished. In Case 3 preliminary radioscopy of the abdomen revealed the distended coils of the colon, and it must be emphasized that in the examination of such cases special care should be taken to demonstrate the full capacity of the colon; several quarts of barium sulphate are often necessary for this purpose, and the use of a barium enema of the usual size may lead to the true degree of dilatation being overlooked (Plate 42, Fig. 16).

Extreme dilatation of the colon was described by Langmead in 1911 in a series of cases of 'colonic tetany'. No observations on the chemistry of the faeces or blood were included, but post-mortem reports on several cases were given; in the light of present knowledge it seems clear that the condition described by Langmead was identical with that forming the subject of the present communication. Marked dilatation of the colon has been recorded in one case by Miller (1923). Taylor (1922) found distinct dilatation of the colon in each of seven cases examined by means of barium enemata. Linder and Harris (1930) record dilatation in one of their cases, and it was also observed by Holmes and Starr (1929). The theory of Miller that this finding is due to kinking of the colon seems scarcely tenable in view of the gradual evolution of megacolon which can be traced in the present series.

A definite relationship appears to exist between diarrhoea and dilatation of the colon. Thus, Cases 7 and 14, in whom diarrhoea was present during observation, exhibited no colonic dilatation; whilst, with one exception, those in whom actual megacolon was present had no diarrhoea, and those in whom the colon was moderately dilated showed very little diarrhoea.

We can find in the literature of megacolon no reference to coeliac disease as a cause of this condition, the vast majority of observers holding that some factor causing difficulty in releasing the muscles controlling evacuation of the large bowel or actual mechanical obstruction is the all-important cause in cases with marked megacolon. Cases such as those here recorded are of importance as indicating that chronic gaseous distension of the large bowel, possibly with an attendant atony of the gut, is a potential cause of extreme and probably permanent dilatation.

A further important consideration in connexion with the occurrence of dilatation of the colon in cases such as these is its value as an indication of intestinal intoxication. Until the close relation between tetany and hypocalcaemia had become revealed by improved methods of blood analysis, intestinal toxæmia appeared to be a likely explanation of this symptom. This hypothesis was advanced in the series of Langmead (1911), but appears to be a less probable explanation in the light of present knowledge. Schaap (1923, 1926) may be mentioned as an authority who has supported Herter's (1908) belief in the great importance of intestinal toxæmia as a cause of the infantilism of coeliac disease; it is interesting to note that the case of 'infantilism from chronic constipation' which he quotes in support of this theory had megacolon, and in the absence of evidence as to the fat content of the faeces in that case it seems possible, in view of our own experience of the suppression of diarrhoea following secondary dilatation of the colon

in this disease, that this case was in reality a case of infantilism secondary to masked steatorrhoea.

Whether or not it is correct to interpret the dilatation of the colon as a protective mechanism which delays the evacuation of the faeces and so checks the diarrhoea, it is true of the majority of cases that diarrhoea tends to become inconspicuous although chemical examination reveals that the stools remain fatty.

(e) *The character of the stools.* In the fifteen cases forming our series there was a history of long-standing diarrhoea in twelve, dating from early childhood in ten, and arising in recent years in one. But in only five was diarrhoea a recognizable clinical manifestation during the periods when they were under our observation (Table I). As these patients were on the average observed for eighteen months or longer, it becomes evident that in adolescents and adults diarrhoea is very frequently absent, although a history of it can always be obtained. It must further be noted that the history given by the patient alone must be accepted with considerable reserve; for example, in Case 3 of our series, in whom intestinal manifestations were very prominent, the patient denied having ever had diarrhoea, and it was only on questioning her mother that we learnt of her past history of many years in hospital in infancy and early childhood when diarrhoea was present off and on in a most striking degree.

TABLE III
Percentage of Fat in Dried Faeces

Case No.	Total fat.	Unsoaped fat.	Neutral fat.	Free fatty acid.	Combined fatty acid.
1	63.9	30.8	2.9	27.9	33.1
2	56.2	19.9	7.2	12.7	36.3
3	61.1	22.0	5.8	16.2	39.1
4	50.7	31.6	4.7	26.9	19.1
5	59.5	33.6	21.3	12.3	25.9
6	60.4	51.8	42.2	9.6	8.6
7	47.1	16.5	6.8	9.7	30.6
8	71.2	67.0	45.2	26.0	4.2
9	60.0	40.0	19.3	20.7	20.0
10	55.5	38.4	10.0	28.4	17.1
11	48.7	24.2	11.1	13.1	24.5
12	67.5	18.0	2.1	15.9	49.5
13	45.6	38.7	13.3	25.4	6.9
14	50.7	31.2	8.8	22.4	19.5
15	52.4	27.0	—	—	—

Chemical examination of the faeces in our cases disclosed that, in spite of this frequent absence of diarrhoea, steatorrhoea was present in every case. Full details of the chemistry of the faeces are given in Table III, from which it will be seen that a high total percentage of fat, chiefly in the form of split and neutralized fat, was the chief feature of the chemical analysis. From this it would appear that dehydration of the stools rather than improved fat digestion or absorption is the reason why diarrhoea tends to disappear in adolescent and adult life.

This abnormality of the chemistry of the faeces is, in spite of the absence of diarrhoea, often revealed clinically by the bulk or the pallor of the excreta, and careful clinical observation of this should be sufficient to arouse suspicion of steatorrhoea even when diarrhoea is absent.

The voluminous, pale, frothing, and offensive stools were the cardinal manifestation of the disease emphasized by Gee in his original description. The pallor was the reason for the belief of Cheadle (1903) that lack of bile was the predominant aetiological factor, although Gee (1888) states that 'the paleness is commonly supposed to signify lack of bile; but the colour of faeces is a very rough measure of the quantity of bile which they contain'. His contention has been proved correct, but later writers, particularly Miller (1923, 1926), have emphasized that there is not infrequently a non-diarrhoeal type of coeliac disease in which the faeces are well coloured and not gaseous, although still bulky. Schaap (1926) states that the whiter stools take on a normal colour when exposed to air, owing to the oxidation of stercobilin.

Heubner (1909) was among the first to recognize that the foaming character of the stools was not a constant accompaniment of the disease. German writers in particular have recognized that this symptom is probably the expression of the putrefactive decomposition of carbohydrate by intestinal bacteria, whereas the less gaseous and more obviously greasy stools are the result of the malabsorption of fat, for dietetic or other reasons, becoming the more prominent feature of a particular case. Holt (1926) and Taylor (1922) may be cited as authorities who have stressed the importance of such carbohydrate fermentation.

Tropical sprue, which in many of its manifestations, notably steatorrhoea, tetany, and anaemia, so closely resembles coeliac disease, is characterized by the occurrence of stools the foaming character of which is even more marked than in the most active diarrhoeal examples of coeliac disease. Such stools have been compared, in their appearance, to soda water. The severity of this characteristic is an important diagnostic point.

We are of opinion that gas production of this type is probably the chief factor responsible for the abdominal distension seen in these cases, and that it is due to the production of gas from carbohydrate by bacteria. Such a view does not carry with it the implication that grossly pathogenic bacteria are present. Schmidt and Strasburger (1901), Strasburger, Strauss, and Marx (1927), Hurst and Knott (1931) have emphasized, apart from coeliac disease, the importance of such carbohydrate indigestion, and the more reasonable deduction is that such a condition implies an impairment of the normal secretion of amylolytic enzymes into the small intestine.

Reference has been made in the historical section of this paper to the cases described by Bramwell (1902-1915) as 'pancreatic infantilism'; study of his writings suggests that whilst some of his cases were possibly examples of pancreatic deficiency in childhood, others were identical with those of our series and in them there was no demonstrable pancreatic lesion.

Reference must also be made to the condition described as 'congenital steatorrhea', which is characterized by the passage of butter-like stools, and has been included by Garrod (1923) amongst the inborn errors of metabolism. This rare condition has long been known to physicians, a list of classical writers who have described it being given by Elliotson (1833). In addition to Garrod's cases others have been studied by Miller and Perkins (1923), and Spriggs and Leigh (1916), in recent years. Such observations have never included mention of infantilism, bony changes, tetany, or anaemia, and so far as we can ascertain the condition is not related to the one at present being described.

VI. *Nervous Phenomena*

The infantilism which places so definite a stamp on the osseous and general development of these patients is to be found reflected in their mentality. It is well known that the child with coeliac disease is often irritable and exacting though not lacking in intelligence. This curious mental state was seen in many of our cases, but it must be remarked that several of them appeared perfectly normal, and in assessing their general mental condition allowance must be made for the fact that nearly all of them had suffered many years of invalidity, and so had not led a normal life as regards association with their fellow beings.

By far the most important fact in connexion with the nervous system is the occurrence of tetany. This is too well known in infantile coeliac disease to call for comment, but it is important to emphasize that in our group latent or acute tetany occurred in every case save one (Table IV).

Acute manifestations lead many of these cases to present themselves at neurological hospitals: others are at times unable to follow their normal occupation on account of severe muscular cramps, a good example being Case 7, who was obliged to give up piano-playing for this reason. Apart from such acute symptoms, inquiry into the history in nearly every case revealed that at times cramps of greater or less severity had occurred. Several of our patients volunteered the information that after writing for a relatively short period they would be obliged to cease on account of the spasm of the muscles of the hands; others described spasm of the leg muscles which would hinder them from walking more than a short distance. The manner in which one of these patients, even when still young, will when asked give an imitation of severe carpo-pedal spasm, is very vivid. In addition to symptoms of tetany, physical signs were present in the majority of cases in our series; nine of them gave a positive Chvostek sign, and in six the Trousseau sign was positive (Table IV); in only three cases were both signs present simultaneously, and we have not been able to determine why one rather than another of these signs should be demonstrable in a given case.

Chronic diarrhoea as a cause of tetany was noted by Trousseau (1867), but the first report of a case in which fatty stools and tetany were observed in an adult seems to be that of Sonrier (1877). Mention has already been made of the series of cases with marked distension of the colon and tetany reported by Langmead (1911), to whom must be given the credit for the first extensive observations of this character. Findlay and Sharpe (1920) made a full study of one case, aged 52, including observations on the calcium metabolism; they noted a subnormal calcium retention, but claimed an increased excretion of guanidin as the most important factor. Lichtenstein (1921) recorded tetany in four out of nine cases of apparent coeliac disease in adults, and Blumgart (1923) reported three cases of chronic steatorrhoea in adults; in two of these achlorhydria was present, and in two tetany was demonstrable; a full account is given of the curious anaemia, dilatation of the colon was noted in two cases, and the differentiation of the stools from the enormous foaming stools of sprue was commented on. In the same year Tileston and Underhill reported one case, also in America.

TABLE IV

Manifestations of Tetany

Case No.	History of acute tetany.	Chvostek sign.	Trousseau sign.	Serum calcium.*
1	+	+	-	8.6
2	-	+	-	8.7
3	-	+	-	8.0
4	-	-	-	9.8
5	+	-	-	9.0
6	-	+	-	9.0
7	+	-	+	7.9
8	+	+	+	8.4
9	+	-	+	8.2
10	-	+	-	10.1
11	+	+	+	5.1
12	+	-	-	8.6
13	+	+	+	5.9
14	+	+	-	8.6
15	+	-	+	6.3

* Serum calcium figures are in most cases the average of a number of observations.

In 1927, Snell and Habine reported a further case and discussed the association of tetany with chronic diarrhoea, including a full commentary on the literature. The monograph of Lehndorff and Mautner appeared in the same year, and was summarized and discussed in America by Levinsohn. These writers, whilst noting the association between steatorrhoea and tetany, expressed doubt as to its significance in that all of them discussed the possibility of endocrine defects, and especially parathyroid abnormalities, as probable aetiological factors.

Holmes and Starr (1929) made complete observations on five cases in adults characterized by emaciation, anaemia, tetany, chronic diarrhoea, and malabsorption of fat. With one exception, tropical sprue could scarcely be considered as a possible cause in these patients, they were substantially

similar to those reported in this communication; the marked enlargement of the colon, the curious anaemia, tetany, and osteoporosis, are all commented on. In several cases parathormone was employed in order to control the tetany. Achlorhydria was present in one out of the five cases.

Linder and Harris (1930) published a full description of metabolic studies on three cases. One of their cases was an example of tropical sprue, but the others were adults with a very long history of fatty diarrhoea, recent severe tetany, hypochromic anaemia, hypocalcaemia, and dilatation of the colon. They entered into a detailed discussion of the metabolism of these cases. A further interesting case was reported by Marble and Bauer (1931).

All the above observations appear to have been made on cases aetiologically and pathologically similar to those which form the subject of the present communication. In addition it must be noted that the association of tetany with tropical sprue, if somewhat rare, is well known. Cantlie (1913), Bassett-Smith (1919), Harrison (1913), Barach and Murray (1920), Bovaird (1921), Scott (1923), Jamieson (1923), Thaysen (1926), and Fairley (1930), have all recorded such cases. Ashford and Hernández (1926) found hypocalcaemia in certain cases of tropical sprue, whilst Baumgartner and Smith (1927) made the same observation in eight out of fifteen cases studied.

In spite of the numerous references given above it must not be assumed that chronic steatorrhoea accounts for a high proportion of all the cases of tetany seen in this country or, indeed, in Western Europe or the United States. Possibly in climates where tropical sprue is prevalent it is more frequently encountered, but the comment in the papers by Howard (1906), Howland and Marriott (1917), and Snell and Habine (1927), on the relative rarity of fatty diarrhoea as a general cause of tetany is undoubtedly accurate.

VII. *Anaemia*

As already mentioned, anaemia is one of the classical symptoms of coeliac disease, described by Gee (1888) in his original description of the condition. Severe anaemia was the presenting symptom in only one patient in the present series, Case 8, who was admitted to hospital on one occasion with severe dyspnoea and weakness. Transfusion was considered on more than one occasion during the earlier observations of Case 2, as the anaemia was so definite. It is probable, however, that the lassitude, which is a constant complaint, is due in part to long-standing haemoglobin deficiency.

Blood picture. Detailed haematological investigations were made in twelve cases of the present series. The red cells are affected to a much greater extent than the white cells. A leucopenia or normal white count is usually found showing no significant variation in the differential cell count or appreciable shift in the Arneth count. A leucocytosis only occurs in intercurrent infections (Fanconi, 1928, Hablützel-Weber, 1923). A study of our series of cases shows that one of the following blood pictures may occur: (i) Normal;

(ii) hypochromic anaemia; (iii) megalocytic hyperchromic anaemia; or (iv) erythroblastic anaemia.

Careful examination of the literature confirms the occurrence of these four types.

(i) *Normal blood picture.* Three patients in the present series had normal blood pictures throughout the period of observation (Table V). Case 15, who died in an emaciated condition, following prolonged diarrhoea, showed no blood changes, nor did Cases 10 and 11. Holmes and Starr (1929) and Fanconi (1928) report similar cases.

(ii) *Hypochromic anaemia.* The patients in this group may have either a normal total red cell count and diminished haemoglobin, or both elements may be reduced (Table V). The haemoglobin is always diminished to a greater extent than the red cells. Iron deficiency in the diet has been shown to be an extremely common cause of hypochromic anaemia in infancy (Mackay, 1931). Anaemia, therefore, of this type occurring in young children with coeliac disease may be due to other causes than the intestinal disturbance. In discussing the haematological findings Fanconi (1928) alone seems to have realized the possible aetiological importance of defective feeding which may account in part for the apparently higher incidence of this type of anaemia in young children than in adults. Fanconi (1928) describes twenty-five cases with a haemoglobin below 60 per cent. Hablützel-Weber (1923) reports one case where the haemoglobin varied between 25 per cent. and 30 per cent. Constam and Partch (1929), Herter (1908), Pipping (1923), and Lichtenstein (1921) describe a similar type of anaemia, while Still (1918), in discussing the haematology of coeliac disease, claims that the only constant change is a diminution of haemoglobin. Thaysen (1931) records a hypochromic anaemia in twenty out of twenty-nine patients, but does not discuss the appearance of the red cells. Other observers report similar findings (Tileston and Underhill, 1923, Whipple, 1907).

Five patients in the present series showed diminished haemoglobin values (Table V), Cases 3, 9, 12, 13, and 14. One gave a history in the past of severe anaemia, 'almost pernicious anaemia', successfully treated with liver, but no details could be obtained. The red cells showed considerable anisocytosis. In all cases there was a number of megalocytes. Measurement of the red cells in Case 3 gave a mean diameter of 7.578μ , which though within normal limits is well to the right of the average normal, 5.6 per cent. megalocytosis and a variability of 10.2 per cent., which is definitely greater than normal. The indirect van den Bergh reaction was negative in all cases.

Treatment. This type of anaemia was resistant to marmite given in large doses for a period of four weeks. It responded extremely well to massive iron dosage in two cases and less well in a third. In Case 14 the haemoglobin, which had been constant over an adequate control period, rose from 34 per cent. to 80 per cent. within four weeks. In Case 9, where a hypochromic anaemia had been present for at least eighteen months, the

haemoglobin rose from 58 per cent. to 88 per cent. in nine weeks. There was a gain of only 14 per cent. in six weeks in Case 3. Further investigations are being carried out on this patient.

(iii) *Megalocytic hyperchromic anaemia*. Nineteen cases of megalocytic hyperchromic anaemia occurring in association with probable cases of coeliac disease have been recorded (Blumgart, 1923; Fanconi, 1928; Hampson and Shackle, 1924; Hablützel-Weber, 1923; Holmes and Starr, 1929; Holst, 1927; Hotz, 1924; Lehdorff and Mautner, 1927; Rossier, 1931; Thaysen, 1931; Vischer, 1923; Witts, 1932), and there are two further cases described by Hegler (1928) and Schäfer (1923) as non-tropical sprue which possibly fall into this group. In neither, however, is mention made of bone changes or disturbance of calcium metabolism.

Two patients in the present series (Cases 7 and 8) had such an anaemia, which, as reported in detail elsewhere, was immediately relieved by large doses of marmite (Vaughan and Hunter, 1932). One of these cases had been successfully treated with liver extract two years previously.

The megalocytic hyperchromic anaemia of coeliac disease appears to be indistinguishable from that occurring in sprue, in tropical megalocytic anaemia, and in association with gastro-colic fistula, but to differ from Addisonian pernicious anaemia. In the first group the indirect van den Bergh reaction is low (Fairley, Mackie, and Billimoria, 1929; Fairley and Kilner, 1931; Vaughan and Hunter, 1932; Wills and Mehta, 1930), poikilocytosis is not a striking feature (Fairley, Mackie, and Billimoria, 1929; Fairley and Kilner, 1931; Vaughan and Hunter, 1932; Wills and Mehta, 1930), free hydrochloric acid may frequently occur and may return on recovery, and the anaemia responds to marmite (Vaughan and Hunter, 1932; Wills, 1931). In Addisonian pernicious anaemia, however, the indirect van den Bergh reaction is high (Fairley, Mackie, and Billimoria, 1929), poikilocytosis is marked, and free hydrochloric acid is extremely rare and does not return on haematological improvement, while marmite has no therapeutic value (Davidson, 1931).

Marmite would appear to affect haemopoiesis only, since the other symptoms, diarrhoea and tetany, were unaffected by its use, while the characteristic flattened sugar curve was still found though the blood picture had returned to normal. Marmite is a complex substance prepared commercially from yeast. It contains all the constituents of the vitamin B complex and small amounts of such things as celery seeds added for flavouring purposes. Experimental evidence in animals as to the effect of vitamin B upon haemopoiesis is conflicting (Guha and Mapson, 1931; Sure, Kik, and Walker, 1929; Sure and Kik, 1931). Clinically, anaemia is not invariably associated with either of the diseases dependent upon lack of vitamin B, namely beri beri (Keefer and Yang, 1929) and pellagra (Boggs and Padget, 1932). If present it is hypochromic in character. Strauss and Castle (1932) have, however, recently shown that yeast is a potent source of the extrinsic factor necessary for reaction with normal gastric juice in order to produce

the principle effective in Addisonian pernicious anaemia: and that this factor is closely associated with, if not identical with, vitamin B₂. Possibly, therefore, in the present cases marmite acts by supplying adequate vitamin B₂ or the extrinsic factor. Since the diets were not previously deficient in vitamin B₂ presumably certain cases require abnormally large quantities in order to obtain any effect, as in the case of the treatment of idiopathic microcytic anaemia by iron.

(iv) *Erythroblastic anaemia*. Cooley (1927) was the first to describe a syndrome, which he called erythroblastic anaemia, occurring in children of Mediterranean stock. It is characterized by a severe anaemia, like that usually described as von Jaksch's anaemia. The blood-films show large numbers of nucleated red cells and occasional immature white cells. The spleen is enlarged; there is a peculiar muddy-yellow pallor of the skin and alterations in the bones leading to a mongoloid type of face and rarefaction of the long bones. Similar cases have since been recorded (Batey, 1930; Capper, 1931; Munford, 1931; Whitcher, 1930; Wollstein and Kreidel, 1930). Fanconi (1928), discussing the type of anaemia that may occur in coeliac disease, mentions that von Jaksch's anaemia is sometimes found, though he gives no details. A case described by Tidy (1920) as infantilism and pernicious anaemia would appear to belong to this group. The patient, a boy aged 13, was sent home from school with a large spleen and a diagnosis of pernicious anaemia. Joint changes, the nature of which are not recorded, were said to have occurred at 4 years of age. The red cells were now about 2,000,000 per c.mm. and the haemoglobin 45 per cent. Myelocytes and myeloblasts as well as primitive red cells were constantly present in the films. This is a most unusual finding in true Addisonian pernicious anaemia, except for a few hours at the beginning of a remission, though it is characteristic of erythroblastic anaemia. Tidy (1920) suggested, since there was no albumin in the urine pointing to a diagnosis of renal dwarfism, that there was an error in the bone-marrow leading to the peculiar changes in the joints and to the error in the blood production.

In the present series two cases (Cases 2 and 6) showed blood pictures that were typical of those seen in erythroblastic anaemia. In addition, Case 6 had the typical triangular-shaped head, with high forehead, prominent frontal bosses and malar bones, and widely-set eyes, that is typical of the condition (Plate 39, Fig. 11). This was present, but not to such a marked extent, in Case 2. Both had a severe anaemia with a low colour index but great anisocytosis, the films showing both megalocytes and microcytes. The megalocytes were extremely pale, almost ring-like, cells and appear to be characteristic of the condition. Case 2 had 3,600,000 red blood-cells per c.mm., haemoglobin 40 per cent., colour index 0.47, and a nucleated red blood-cell count that varied between 182 and 284 per 100 white blood-cells. The majority had small pyknotic nuclei (Plate 43, Fig. 17). Such a high count probably prevents accuracy in the total white cell count, which was about 10,000 per c.mm. Occasional myelocytes were

present. The van den Bergh indirect reaction was negative. Measurement of the red blood-cells gave a mean diameter of 7.695μ , that is within normal limits, but 23.2 per cent. of megalocytes and a variability of 15.9 per cent., a most unusual type of Price-Jones curve (Fig. 18).

Case 6, when first seen by Dr. Davey, had 3,505,000 red blood-cells per c.mm., haemoglobin 38 per cent., colour index 0.54, white blood-cells 6,180 per c.mm., and 173 normoblasts to every 100 leucocytes. A Price-Jones curve showed a mean diameter of 8.0965μ , variability 10.6 per cent., and 22.8 per cent. megalocytosis, figures which are compatible with a diagnosis of Addisonian pernicious anaemia (Fig. 19). The large pale cells, however, and low colour index are never found in the idiopathic type, while Jörgensen and Warburg (1927) have found a megalocytic type of curve in anaemia pseudo-leukaemica of infants or von Jaksch's anaemia. Occasional neutrophil myelocytes were seen. The indirect van den Bergh reaction was negative.

The blood picture in these two cases is thus indistinguishable from that seen in erythroblastic anaemia. The reported cases occurred in younger people unassociated apparently with either tetany or diarrhoea; and there was a fatal termination before the age of 20. There are, therefore, differences between the hitherto reported cases and those in the present series. It would appear reasonable to suggest, however, that as a megalocytic hyperchromic anaemia may occur as a symptom in a variety of conditions associated with disordered gastro-intestinal function so may an erythroblastic anaemia. Cooley is inclined to regard the bone changes in the latter as secondary to a primary disorder of the marrow. The present observations suggest, however, that the two may occur independently though depending upon a common cause, i.e. faulty absorption or production, in the gastro-intestinal canal, of factors essential for normal ossification and haemopoiesis.

Treatment. Case 2 was given marmite 12 grm. daily for six weeks with no appreciable effect on the blood picture. Bland's pill gr. xc daily caused rapid clinical and haematological improvement. The peculiar and characteristic dirty, putty-coloured complexion gave way to a clear pink and white. He felt more energetic and his appetite improved. The haemoglobin rose from 40 per cent. to 90 per cent. in twenty-one weeks, while nucleated red blood-cells were found only rarely in stained films. Case 6 similarly failed to respond to pig's stomach and liver given for a month, but following large doses of iron (ferri et ammon. cit. gr. xc daily) there was great improvement. Three months later the red blood-cells were 5,100,000 per c.mm. and the haemoglobin 70 per cent. The films still showed the characteristic picture. The red blood-cells were variable in size showing many large pale cells and 29 normoblasts per c.mm., a most unusual finding in such a slight degree of hypochromic anaemia unless associated with carcinomatosis. The red cells in the latter disease never show such extreme anisocytosis and megalocytosis.

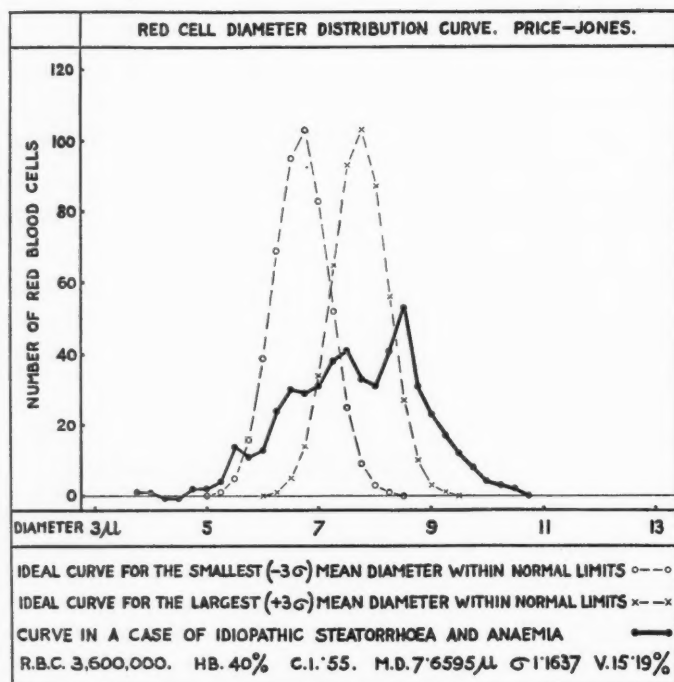


FIG. 18.

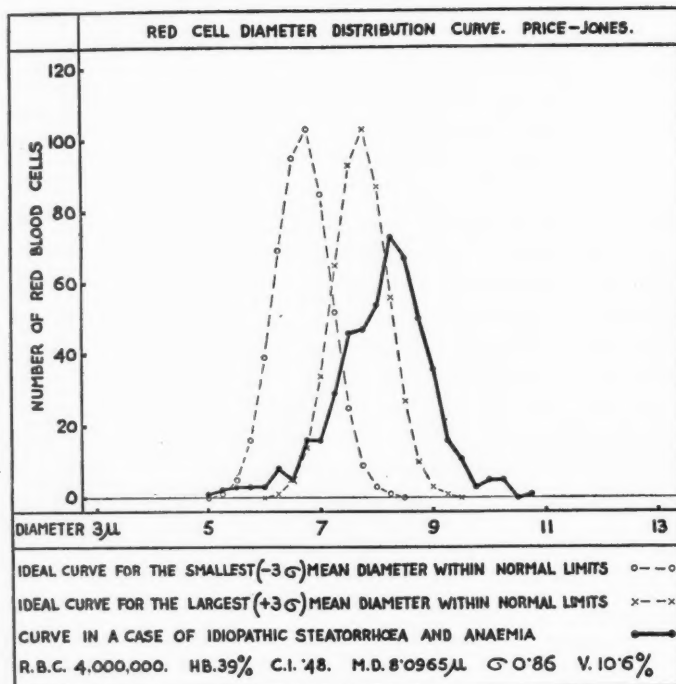


FIG. 19.

Haemorrhagic phenomena. Haemorrhagic phenomena, including haematemesis, epistaxis, and subcutaneous haemorrhages are extremely rare. They have been described chiefly in children, when the symptoms may be due to an associated scurvy. Still (1918) drew attention to his finding of scurvy as an antecedent in four out of forty-one cases, which he thought too high an incidence to be accidental. Its development during the course of the disease he considered probably due to the dietetic measures employed. Certain cases are definitely relieved by antiscorbutic treatment (Fanconi, 1928; Strandqvist, 1929). In others, described by Fanconi (1928) as examples of 'hypothrombinaemia', such therapy is without value. Fanconi believes that in such cases the haemorrhage is due to some specific failure of the ferment of coagulation, since there is no diminution of platelets and the retraction of clot and bleeding time are normal. Four, however, of his five cases had associated infections and the fifth showed *post mortem* cirrhosis of the liver, conditions which are frequently associated with haemorrhagic manifestations. Strandqvist (1929) described a typical case of coeliac disease in a girl of 5½ years who, having failed to react to antiscorbutic treatment, died of gastro-intestinal haemorrhage. No obvious sepsis was present and the *post mortem* examination was negative. This would appear to be the only case recorded associated with otherwise unexplained haemorrhagic phenomena, apart from Holst's case of severe megalocytic anaemia that was found to have a haemorrhage into the jejunum at autopsy. No such symptoms were found in the present series, though two cases were said to bruise easily.

Variability of the anaemia. It is clear that the character of the anaemia is extremely variable, depending presumably upon which of the factors essential for normal haemopoiesis is lacking.

This polymorphic character is not, however, as Thaysen (1931) suggests, peculiar to coeliac disease. It is frequently found when anaemia is associated with gastro-intestinal lesions. Post-gastrectomy anaemias may be either hypochromic, or hyperchromic and megalocytic, while both varieties are found in association with intestinal stenosis (Witts, 1932) and severe diarrhoea due to tuberculosis and dysentery (Keefer, Huang, and Yang, 1929). When changes in type are reported as occurring in the same patient in coeliac disease it is frequently in association with pyrexia or else following treatment. It is well known that acute infections will precipitate a relapse in idiopathic pernicious anaemia and that spontaneous remissions with alteration in the haematological picture may occur. Further, after liver treatment certain cases may develop a hypochromic type of anaemia unless iron is given (Beebe and Lewis, 1931). Thaysen, however, makes no attempt to correlate his blood picture with treatment.

No striking alteration in the character of the blood picture in any one patient was found in the present series apart from a return to normal on appropriate treatment.

TABLE V. *Haematological Picture*

Case No.	Sex & Age	R.B.C. units per c.mm.	Hb. %	C.I.	W.B.C. per c.mm.	Mean diameter R.B.C. μ	Variability R.B.C.	Megalo-cytosis.	Micro-cytosis.	Poikilo-cytosis.	Van den Bergh units.	Test meal.	Glossitis.
1	16 M	4,400,000	75	0.85	8,500	7.6595 μ	15.19 %	23.2 %	3.6 %	0	? +	Free HCl	-
2	26 M	3,600,000	36	0.5	6,400						0.5		+
3	17 F	4,000,000	60	0.75	3,700	7.578 μ	10.2 %	5.6 %		0	0.45	Free HCl	-
4	15 F	5,000,000	82	0.82	17,500							Free HCl	-
5	58 F	4,095,000	85	1.36	7,600							Free HCl	-
6	34 M	4,000,000	39	0.48	7,890	8.0965 μ	10.6 %	33.8 %	0.4 %	0	Negative	Achlor-hydrin	+
7	22 F	2,500,000	52	1.04	2,400	8.115 μ	11.7 %	37.2 %		0	0.75	Free HCl	+
8	40 F	3,300,000	68	1.03	2,400	7.782 μ	9.5 %	8.8 %		0	0.75	Free HCl	+
9	34 F	4,600,000	54	0.5	2,400			0		0	0.15	Free HCl	+
10	19 F	4,900,000	80	0.81	7,500			0	0	0		trace	-
11	36 M	5,000,000	80	0.80	8,800							Achlor-hydrin	-
12	57 F	5,400,000	70	0.63	8,200			0		0	0.25	Free HCl	-
13	19 M	4,500,000	66	0.73	4,200			0	Slight		0.15	Free HCl	-
14	16 M	4,600,000	36	0.39	4,200			v. occasional	0	0	0.35		-
15	58 M	5,000,000	85	0.85	11,120							Trace	+

254 N. red cells per
100 white cells
Anisocytosis

2 N. red cells p
100 white cells
61 N. red cells per
100 white cells
Anisocytosis

Anisocytosis
Anisocytosis

Slight anisocytosis
Slight anisocytosis
Anisocytosis

Anisocytosis

Relationship of the blood picture to other manifestations. Castle and his co-workers (1931) in discussing the relationship of disorders of the digestive tract to anaemia conclude, 'in general it can be shown that patients with diarrhoea are more prone to develop anaemia than patients without diarrhoea'. Thus Keefer (1929) has recently found that the various types of anaemia which may be associated with tuberculous and dysenteric ulceration of the intestine improve when the diarrhoea is controlled. Lehndorff and Mautner (1927) draw the same conclusion in the case of coeliac disease.

A study of the present series of cases suggests, however, that the failure of haemopoiesis is not dependent upon a deficiency brought about by the mechanical action of the diarrhoea in hurrying food along the intestines and so preventing absorption, but rather upon some associated but independent failure of absorption or digestion. Castle and his fellow workers (1931), indeed, have shown that the intrinsic factor may be absent from the gastric juice of cases of hyperchromic anaemia associated with diarrhoea due to sprue or multiple intestinal anastomoses. Case 11, whose history went back to childhood, passed as many as nine stools a day, but while under observation never showed anaemia and gave no history of anaemia. Case 8, on the other hand, lost her megalocytic hyperchromic anaemia under appropriate treatment, though tetany persisted and she passed nine or more stools a day. Case 7 never had prolonged diarrhoea, yet a relatively severe grade of megalocytic hyperchromic anaemia was present.

Apart from the two cases having an erythroblastic anaemia in association with the peculiar deformities of the bones of the skull described by Cooley (1927), there was no correlation between the blood picture and the degree of bony change as evidenced by deformity or by X-ray examination.

Some degree of glossitis is commonly found in association with severe anaemias. It occurred in seven of the recorded cases complicated by a megalocytic hyperchromic anaemia (Vaughan and Hunter, 1932) and was probably found in Thaysen's three cases, since he claims that 79 per cent. of his patients showed some affection of the tongue. Herter also draws attention to its occurrence. In the present series only one patient (Case 7) in answer to a direct question complained of a sore tongue, but atrophy of the papillae or stomatitis was found in five cases, associated with all types of anaemia.

In spite of the frequency of achlorhydria in severe anaemias, it was found in only two of the twelve cases in which it was possible to perform a gastric analysis. One of these cases had no anaemia. It was only noted in three of the nine cases of megalocytic hyperchromic anaemia (Vaughan and Hunter, 1932) associated with coeliac disease which have been previously reported.

It appears justifiable to conclude that the presence of the anaemia and its character in coeliac disease are independent of the other symptoms and arise, as does the anaemia of sprue, from some associated deficiency of one or more of the factors essential to haemopoiesis. The exact mechanism of

this deficiency has still to be determined, but would appear not to be immediately associated with diarrhoea.

VIII. *Metabolic Observations*

A considerable literature has arisen concerning various aspects of the metabolism of coeliac disease and allied conditions, and study of this literature, together with the observations made on our series, brings the conviction that the problems involved are many of them so complex, whilst the manifestations of the disease, whether clinical or biochemical, are so protean, that we are still far from being in the position to pronounce any final judgement concerning the many chemical phenomena involved.

In the present section we record our findings under various headings and have made some attempt to discuss the existing literature in the hope that at a future date these problems will have become less obscure.

(1) *Carbohydrate metabolism.* Reference has been made, in the section dealing with the clinical aspects of the faeces, to the malabsorption of carbohydrate, with bacterial fermentation and gas formation, which is at times a prominent feature of these cases, but which is usually considerably less marked than in tropical sprue; we have stated that it has been seen only in minor degree in the series of adolescents and adults which forms the subject of the present study. It has been pointed out how dilatation of the colon is to some extent a consequence of this dysfunction of carbohydrate digestion, and is also a mechanism tending to mask the consequences of such maldigestion.

Glycosuria was not discovered in any of our cases. Poynton and Cole (1925) have described a case showing glycosuria, but examination of published reports shows that glycosuria is such an unusual finding in coeliac disease and allied conditions that its occurrence cannot be regarded as more than a coincidence.

The accompanying chart shows the effect on the blood-sugar of the administration of 50 grm. of glucose taken when fasting. This test was performed in thirteen of our cases, and it will be observed that in eleven of them the normal rise in blood-sugar did not occur (Fig. 20). It is further notable that the fasting level of blood-sugar was low in a considerable number of our cases (Table VI). Thaysen (1926) was the first to record this curious response to glucose administration; he found a normal response in very few cases, and a slight or negative response in the remainder. Similar observations have been made by Holst (1927), McLean and Sullivan (1929), Fanconi (1928), and Macrae and Morris (1931). Two explanations for this abnormal response suggest themselves. Either absorption from the small intestine is greatly delayed or, alternatively, there is so rapid a storage of glucose in the form of glycogen by the liver that the normal rise in the sugar content of the blood cannot occur. The subcutaneous injection of

adrenalin in these cases produces a rise in the blood-sugar of normal degree, and this together with the absence of evidence in any way suggestive of increased hepatic function makes it improbable that super-storage is a true explanation. That, on the other hand, there is a delay in glucose absorption would seem to be a plausible explanation in view of the obvious difficulty in the absorption of other food constituents by these patients. Against this explanation Thaysen (1929) has argued that observations of

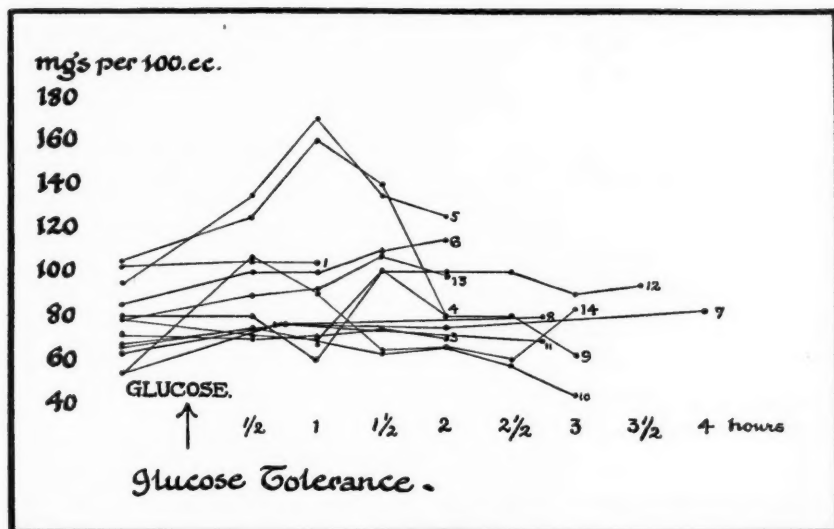


FIG. 20.

the respiratory quotient in various circumstances and the response to the intravenous injection of glucose give results pointing in a different direction. He postulates some endocrine derangement as the explanation of the low blood-sugar curve. We agree with Macrae and Morris that such arguments do not carry conviction. On the other hand, until more exact data are available as to the effect of increased rapidity of movement through the alimentary canal upon the absorption of various substances, including carbohydrate, we feel it would be premature to assume that the 'flat blood-sugar curve' must be accepted as evidence of an actual derangement of the absorptive function of the intestinal mucosa.

(2) *Protein metabolism.* Chemical examination of the faeces in our series of cases has been confined to the estimation of fat and calcium. The literature contains certain observations on nitrogen balance. Herter (1908) found that the absorption of protein was diminished. McCrudden and Fales (1913) found that there was increased nitrogen loss in the faeces, but believed that this was due to a re-excretion into the colon; they found in this a partial but insufficient explanation of the infantilism of coeliac disease; their observations were made upon a single case. Czerny and

Keller and Lehdorff and Mautner (1927) stated that they had found a general diminution of nitrogen metabolism with a high nitrogen content in the stools. Fanconi (1928) also reported a considerable loss of nitrogen in the faeces, but Macrae and Morris (1931) reported a much lower percentage loss, and found, further, that periods when this loss was at all remarkable coincided with periods of markedly defective fat absorption. Schaap (1923-26) found no nitrogen loss in the faeces beyond what is to be expected when bulky, fatty stools are prominent.

TABLE VI
Chemistry of Blood

Case No.	Serum calcium.	Inorganic phosphorus.	Plasma phosphatase.	Blood-urea.	Blood-sugar.	Cholesterol.
1	8.6	5.3	1.06	17	102	117
2	8.7	3.4	0.406	16	104	115
3	8.0	4.4	—	19	98	145
4	9.8	5.5	—	25	100	—
5	9.0	5.9	—	20	85	135
6	9.0	4.3	—	24	100	200
7	7.9	2.5	0.305	18	83	—
8	8.4	3.0	0.283	20	80	—
9	8.2	2.4	0.540	28	80	—
10	10.1	2.5	0.202	22	74	—
11	5.1	2.3	0.345	21	77	—
12	8.6	2.3	0.718	—	100	—
13	5.9	5.8	0.425	35	175	—
14	8.6	2.3	0.645	37	105	—
15	6.3	2.3	0.241	30	80	—

Except in the case of phosphatase the above figures represent milligrammes per 100 c.c. of blood.

In several of our cases, notably Case 3, observations of the urea and non-protein nitrogen content of the blood on many occasions showed this to be below what is normally encountered in the average healthy individual. The accompanying chart shows the readings for urea and non-protein nitrogen in Case No. 3, taken at frequent intervals over a long period (Fig. 21).

As during the time these observations were made this patient was taking a diet very low in fat and containing considerably more than 100 grm. of protein daily, some significance must be attached to this finding. In the same patient it was found exceedingly difficult, by urea administration, to obtain a urine containing more than 1.5 per cent. of urea, although by no other test, clinical or laboratory, was anything found suggestive of renal impairment.

(3) *Fat metabolism.* In Table III will be found the results of the analyses of the faeces in our series as regards their fat content. Examination of these figures shows that they are in agreement with the majority of the published analyses in cases of coeliac disease in children. That is to say, steatorrhoea is a notable feature but the fats are well split.

The literature reveals an important controversy as to whether such analyses suggest defective absorption of fat in spite of efficient hydrolysis, or whether they represent a massive re-excretion of fat into the colon after relatively normal absorption from the small intestine. Fanconi (1928) is the chief exponent of the latter theory and has sought to prove that when such cases are placed on a very low-fat intake the daily excretion continues not only to equal, but to exceed the amount ingested.

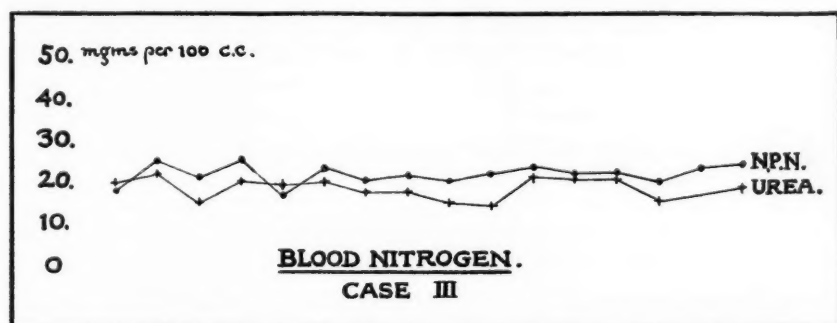


FIG. 21.

In Case 1 of our series a special investigation of this point was made and Table VII shows the percentage of fat in the stools at times when this patient was on ordinary hospital diet, and also during a period when he was kept on a diet containing a very small amount of fat daily. It will be

TABLE VII

Case 1. Percentages of Fat in Faeces

(a) On ordinary hospital diet.

Date.	Total fat.	Unsoaped.	Free F. acid.	Neutral.	Comb. F. acid.
27.8.30	63.9	30.8	27.9	2.9	33.1
6.9.30	52.4	24.8	14.7	10.1	27.6
19.11.30	39.2	21.6	16.2	5.4	17.6
20.11.30	43.3	22.6	18.2	4.4	20.7
21.11.30	47.6	21.8	17.3	4.5	25.8

(b) On low-fat diet (bananas, skim milk, fruit, green vegetables, bread and jam).

19.1.31	35.4	14.3	11.6	2.7	21.1
22.1.31	16.6	7.8	6.8	1.0	8.8
27.1.31	20.8	8.3	6.8	1.5	12.5
28.1.31	23.4	14.8	11.6	3.2	8.6
29.1.31	30.7	12.9	11.2	1.7	17.8
30.1.31	30.3	14.3	11.6	2.7	16.0
31.1.31	24.0	10.3	8.9	1.4	13.7

seen that even during the latter period fat formed on the average more than 25 per cent. of the total weight of the dried faeces.

Special investigation of this was made for us by Professor E. C. Dodds,

who reported, during a period when the patient was on strict low-fat diet, that a 24-hour specimen of faeces gave the following figures: total weight of faeces (dry) 77.1 gm., total fat 23.7 gm., unsoaped 10.0 gm., free fatty acid 8.7 gm., neutral fat 1.3 gm., combined fatty acid 13.7 gm.

These figures would appear to support those of Fanconi, but interpretation of them at the present moment is impossible. Sperry and Bloor (1924) in a careful study of normal animals found that there was almost as much fatty material in the faeces on a fat-free diet as on a fatty diet, and that the nature of the various fractions was similar under the two conditions. They found moreover that the composition of the fat in the diet was always radically different from that of fat recovered from the faeces, although the latter could to some extent be modified by changing the former. They found, on the other hand, that there was a much closer similarity between the chemistry of the fats recoverable from the blood and those recoverable from the faeces.

It is clearly impossible to draw final conclusions at the present time. Schaap (1923, 1926) and Macrae and Morris (1931) consider that malabsorption remains the most probable explanation of the fatty stools seen in coeliac disease. The latter workers, in a series of observations of peculiar thoroughness, reached the conclusion that, at any rate during periods of relative convalescence, an increase in the fat intake in patients with coeliac disease led to an increase in the total fat absorbed. Our own experience is that the fat intake can never be increased to the normal figure for the average healthy individual without risking a relapse of steatorrhoea.

(4) *Calcium and phosphorus metabolism.* That the serum calcium is nearly always found to be low, both in children with coeliac disease and in adults of the type described in this paper, seems agreed by all writers. This is clearly the basis of the tetany so frequently found in these patients. The occurrence of tetany with a low serum calcium is less common in tropical sprue. It has been found that even severe and cachectic cases of sprue often have a normal serum calcium (Ashford and Hernández, 1926).

A low plasma phosphorus appears to be as characteristic of the condition as a low serum calcium, though few authors have paid attention to this. Blumgart (1923) recorded low serum phosphorus in his cases. Parsons (1927) states that 'the bone deformities of coeliac infantilism are rachitic in nature. Although the blood phosphorus is low the rickets is of the low calcium type; which is the explanation of the frequent occurrence of tetany.' Linder and Harris (1930) point out that the scanty urinary excretion of phosphorus found in their cases is accounted for by the fact that the serum phosphorus figure is below a certain threshold.

From their studies of 'non-tropical sprue' Marble and Bauer (1931) and Aub and others (1932) conclude that the low serum calcium and phosphorus, the osteoporosis, and the tetany are due to the inadequate absorption of calcium and phosphorus from the gastro-intestinal tract because of the diarrhoea.

For obvious reasons calcium balance estimations preceded investigations of the blood calcium in point of time. In the cases which he investigated Herter (1908) attributed the infantilism in part to the failure of absorption of calcium owing to its excessive loss in the faeces as soaps. In their description of a case of coeliac disease in a boy of ten McCrudden and Fales (1912) related the osteoporosis and fractures to the negative calcium balance which they found.

In 1920 Barach and Murray attributed the tetany in a case of sprue to calcium deficiency. They held that this arose from interference with calcium absorption by the excess of fat in the stools and from excessive elimination of calcium due to intestinal irritation caused by diarrhoea. Findlay and Sharpe (1919) investigated a case of adult tetany and found a subnormal retention of calcium associated with a diminished absorption of fat.

Telfer (1928) demonstrated grossly defective absorption of mineral elements in coeliac disease in infants; and he found that in this condition calcium is excreted chiefly in the faeces as insoluble soaps. In his various studies of calcium and phosphorus metabolism he showed that one of the important factors influencing the mode of excretion of calcium and phosphorus is the concentration of fatty acids in the intestinal contents. He argued that normally the excess of calcium combined with phosphate and, therefore, in the fatty diarrhoeas a surplus of phosphate remained and was absorbed; but since phosphate could not be retained without calcium it was re-excreted into the urine. Since he found the ratio of urinary to faecal phosphorus to be greater than normal he concluded that 'the conditions which permit of a persistent excess of free fatty acids in the intestine facilitate the absorption of phosphorus'.

Linder and Harris (1930), in a study of three cases of chronic diarrhoea with tetany, produced figures which throw grave doubt upon this hypothesis. They found that both the serum phosphorus and the urinary phosphorus were much lower than in normal individuals, and they therefore postulated a defect in mineral metabolism affecting the absorption of phosphorus. The same authors conclude from the small amount of soap in many of their faecal analyses that calcium soaps cannot be an important factor in preventing calcium absorption. They point out that the association of better calcium utilization with decreased fat excretion suggests that the fat may physically interfere with calcium absorption, or that changes in intestinal absorptive power affect both substances independently.

They also adduce evidence that failure to absorb vitamin D may be the chief factor concerned. They emphasize in this connexion the swift and striking effect of irradiated ergosterol on the tetany, blood chemistry, and calcium and phosphorus balance in their cases, especially during a fat-poor diet. 'The decisive action was therefore to enable the serum to hold a larger amount of calcium and inorganic phosphorus, which is exactly the effect of vitamin D.'

In thirteen out of fifteen cases the serum calcium was constantly below

normal (Table VI). Occasionally, as in Case 11, the level was as low as 5 mg. per 100 c.c., and then tetany was often severe. The plasma phosphorus figures were usually normal or below normal, except in five cases where the reading was above 5 mg. per 100 c.c. We have no explanation to offer for such a wide range of variation. It is conceivable that hypoparathyroidism

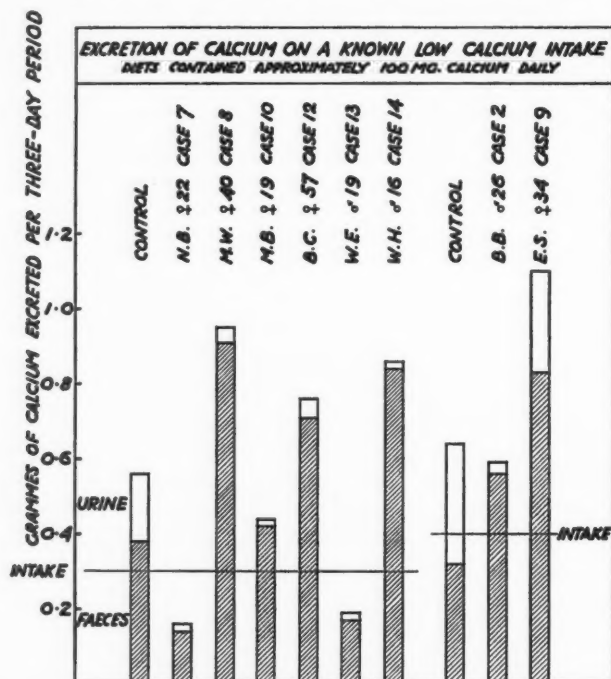


FIG. 22. Calcium balance in idiopathic steatorrhea. The calcium excretion was estimated on a known low calcium intake. The horizontal line represents the calcium intake which was approximately 100 mg. daily. The urinary calcium excretion is represented by unshaded columns and the faecal calcium excretion by shaded columns.

plays some part in keeping the phosphorus level high in certain cases. All the available evidence points to the absence of any endocrine factor as a primary cause of the disabilities seen in our group of cases. The evidence is in favour of defective absorption from the alimentary tract, and if any hypoparathyroidism be present we would stress that it must be a secondary phenomenon.

The plasma phosphatase was estimated in eleven of our cases and found to be high in four. It is approximately true of these cases to say that the severity of the bone disease was roughly proportional to the height of the plasma phosphatase. Thus Cases 3, 12, and 14 were crippled by reason of the pain and deformities of osteomalacia and they show the highest plasma phosphatase readings.

Estimations of the calcium balance were made in eight of our cases (Fig. 22). A low calcium diet was used, and estimations of the calcium output were made both in urine and in faeces. In half the cases examined the total calcium output was greater than in controls: in two cases the total output was normal and in the remaining two below normal. The discrepancy in these figures is more apparent than real, since no allowance has been made for the weight of the patients. Thus Case 12 weighs 7 st. 11 lb. whereas Case 13 weighs only 4 st. 1 lb. The striking fact about the figures for the calcium balance is that the urinary output is relatively so small and the faecal output so large. This corresponds to the findings of many other investigators quoted above. It is, of course, due to the fact that the unabsorbed fatty acids in the alimentary tract combine with calcium salts to form soaps, thus fixing the calcium in the faeces.

IX. General Discussion

1. *Relationship of idiopathic steatorrhoea to tropical sprue.* Reference has already been made to the many similarities between our cases and cases of tropical sprue. Gee (1888) noted this resemblance in his original communication, and the identity of the two diseases has been argued by many subsequent writers, especially Thaysen. Whilst it is true that steatorrhoea, carbohydrate dyspepsia, meteorism, tetany, and anaemias of various types are common to the two diseases, it remains indisputable that, whereas coeliac disease usually arises in young children, tropical sprue almost invariably begins in adults.

A few cases are to be found where the symptom-complex under discussion seems to arise in European countries during adult life; Thin (1889-90), van der Scheer (1918), Nolen (1918), Hegler (1928), Richartz (1905), Schäfer (1923), Holst (1927), Blumgart (1923), and Thaysen (1929, 1931), have all described such cases. Case 12 in our present series might be claimed as representative of such a group, but our personal experience of the frequency with which interrogation of the parents reveals a far longer history than had previously been suspected, leads us to believe that the appearance of this disease for the first time during adult life must, in European countries, be regarded as an extremely rare occurrence. We doubt whether there is justification for a separation of non-tropical sprue from coeliac disease, but on the other hand we feel that coeliac disease and tropical sprue are separate, though closely similar, entities.

2. *The pathogenesis of idiopathic steatorrhoea.* To Gee the 'coeliac affection' was essentially a diarrhoeal disease; there is little doubt but that he would have classed it with the diseases of the alimentary canal. In young children no other conclusion is likely to be suggested, but when a series such as ours, consisting of adolescents and adults, is examined, the major signs and symptoms such as bone deformities, severe anaemias, or tetany, may

lead to a search for another explanation. Especially is this the case when steatorrhoea, though present, is so obscure as to be inconspicuous. We are of opinion that close examination still points to the conclusion that this is a disease of gastro-intestinal origin.

Attempts to demonstrate an anatomical lesion have up to the present failed. This has led to an endeavour to find support for the theory that some endocrine disturbance is the true explanation of coeliac disease. The peculiar response to glucose administration has been held by Thaysen (1929) to supply evidence of some defect of endocrine function; we have given the reasons why we consider this argument unconvincing. Again the derangement of calcium metabolism, of which the outstanding expression is the reduction of the calcium content of the blood, is responsible for two of the cardinal manifestations of this disease, namely osteomalacia and tetany. This fact has led many observers to postulate some derangement of parathyroid function. Thus, Findlay and Sharpe emphasized the supposed disturbance of guanidine metabolism, whilst Schaap (1926), Linder and Harris (1930), and many others, have supported an endocrine hypothesis.

Increased knowledge of the parathyroid mechanism, which has emerged from the study of the effects of the parathyroid hormone and of the phenomena associated with clinical hyperparathyroidism and hypoparathyroidism, makes the existence of any such endocrine factor seem improbable.

TABLE VIII

Hypoparathyroidism.	Coeliac disease.	Hyperparathyroidism.
Low serum calcium	Low serum calcium	High serum calcium
High plasma phosphorus	Variable plasma phosphorus	Low plasma phosphorus
Low urinary calcium	Low urinary calcium	High urinary calcium
No changes in bones	Failure of storage of calcium in bones (osteomalacia)	Bones depleted of calcium (Generalized osteitis fibrosa)
Normal alimentary function	Deranged alimentary function	Normal alimentary function
Tetany	Tetany	No tetany
Opacities in the lens	Opacities in the lens	No lens opacities

Table VIII sets out the main phenomena in these three diseases. Many resemblances are apparent between coeliac disease and hypoparathyroidism, but the former differs from hyperparathyroidism in all particulars.

In the section dealing with fat metabolism we have alluded to the theory of Fanconi (1928) who has said that absorption of fat is normal but that this fat is subsequently re-excreted in pathological degree into the colon. Knowledge of the physiology of fat absorption is not yet sufficient to enable this theory to be assessed properly. We have pointed out how the work of Sperry and Bloor (1924) on normal animals indicates that the observa-

tions of Fanconi do not provide real evidence in favour of his theory, and although it is similarly possible to formulate an explanation, other than malabsorption, to account for the hypocalcaemia of coeliac disease, the hypothesis here again is ingenious rather than convincing. When, on the other hand, the steatorrhoea, the hypocalcaemia, the 'flat glucose tolerance curve', and the evidence of nutritional disturbance provided by the various anaemias, are considered as a whole, it becomes almost impossible to escape the conclusion that coeliac disease is a nutritional disturbance of gastro-intestinal origin dependent upon disturbance of function in spite of the absence of anatomical lesions.

Recent work on Addisonian pernicious anaemia and sprue, where the symptom-complex is as varied as in coeliac disease, has demonstrated that, in these conditions, a specific failure of gastro-intestinal function, not necessarily associated with demonstrable anatomical lesions, is the essential aetiological factor. Castle and his co-workers (Castle, 1929; Castle and Townsend, 1929; Castle, Townsend, and Heath, 1930) have found that in such cases some principle essential for gastric digestion of protein is absent from the gastric juice even when it appears otherwise normal. This deficiency is further complicated in some instances with a failure of absorption, which has been demonstrated experimentally (Castle, Heath, and Strauss, 1931). Apart from Barnett (1931), in whose paper the diagnosis of a test case might be questioned, all other workers substantiate Castle's hypothesis of the extreme importance of gastro-intestinal function in the aetiology of these diseases.

In Addisonian pernicious anaemia and sprue all symptoms are relieved, though to an unequal degree, by the active principle of liver. In coeliac disease, as already discussed, one symptom may be cured by a specific remedy without affecting the others, as for instance the hypochromic anaemia by iron, which suggests that in the latter condition failure of absorption rather than some single fault in digestion is the predominant aetiological factor.

It appears to us, therefore, that the explanation of the cases in our series, some of them crippled or deformed by the effects of osteomalacia, others incapacitated by tetany, and others threatened with death owing to the severity of their anaemia, lies in the fact that they are starving in the midst of plenty. Often not one but several essential nutritional factors are missing, and however dexterously the diet may be adjusted it remains in many cases impossible to maintain the patient in a condition of health.

X. *Treatment*

Our experience with the fifteen cases forming this series has been that treatment presents great difficulties. We have endeavoured, in preceding sections of this paper, to show that probably malabsorption of various foods

is responsible for the major manifestations of the disease and, whilst nothing can at present be done to remedy the primary defect of the alimentary canal, much care is necessary in order to mitigate, as far as possible, the consequences of this defect.

The major therapeutic indications are: 1. Control of the steatorrhoea by a low-fat diet. 2. Control of carbohydrate dyspepsia by regulation of the intake of starch. 3. Relief of tetany by increasing the intake of calcium and of vitamin D. 4. Relief of the pain, and to some extent the bone deformities of osteomalacia by the same means. 5. Alleviation of anaemia, in its various aspects, by increasing the intake of such substances as iron, marmite, or liver.

Our experience is that these patients can seldom be given fat in the amounts found in the average diet without risking the occurrence of diarrhoea. We have found no clinical confirmation of the observation of Macrae and Morris (1931) that fat absorption is increased by increasing the fat intake.

When gas formation from carbohydrate fermentation is prominent the intake of starch must be strictly controlled and the administration of diastase may be useful.

A diet of high-calcium content should in all cases be supplemented by the administration of calcium lactate. This is best given fasting in doses of 5 grm. three times a day. We have also employed calcium gluconate and calcium laevulinate in doses of 2 to 6 grm. daily. Small doses of calcium salts are useless in controlling tetany. In emergency calcium gluconate must be given by intramuscular injection, and if this fails slow intravenous injection of 15 c.c. of a five per cent. solution of calcium chloride must be employed. In no case is the use of the parathyroid hormone justified, for doses large enough to control the hypocalcaemia would lead to further depletion of calcium salts from the skeleton. The use of vitamin D or of ultra-violet irradiation, in tetany, should always be considered.

Vitamin D should be given in every case where there are clinical or radiographic signs of rickets, osteomalacia, or osteoporosis. It often relieves bone pain and helps a crippled patient towards recovery, but any relapse of diarrhoea is liable to interfere with its good effects. We have used it in the form of radiostol tablets (British Drug Houses). Each pellet is standardized to contain 3,000 international antirachitic units of irradiated ergosterol. Cod-liver oil or any form of vitamin D in an oily medium is useless in view of the defective fat absorption.

In treating all forms of anaemia it is essential to remember the importance of adequate dosage. Iron or marmite is given according to the type of anaemia present: details are to be found in preceding sections and in the case notes given in the appendix.

In general we have found that the results of treatment are more disappointing in the adolescent and adult cases which we have studied than appears to be the case in younger children suffering from coeliac disease.

Some cases respond far more satisfactorily than others, a fact for which we have found no explanation. In the majority of cases all that is accomplished is the alleviation of one or more symptoms and the temporary arrest of downward progress.

It is none the less gratifying to have seen the great improvement in the anaemia of many of our cases, and the recovery from the pain and disability of osteomalacia in others. We have often noted a great change for the good in the mental outlook of a dwarfed, crippled, and anaemic patient as he was gradually relieved from his disabilities, especially of anaemia.

Summary

1. Fifteen cases of adult coeliac disease or idiopathic steatorrhoea have been studied. All these patients were born in Great Britain and had never resided abroad. They present the following features: fatty stools, dilatation of the colon, tetany, osteomalacia, anaemia, skin lesions, and infantilism.

2. Steatorrhoea and disturbances of calcium metabolism are alone common to the whole group. Changes in the skeleton were found in all cases investigated. Radiograms showed osteoporosis and often florid rickets. In three cases histological examination of portions of bone showed osteoporosis and osteomalacia.

3. Glossitis occurred in five cases, and achlorhydria in two out of twelve cases examined. Six out of eight cases showed dilatation of the colon, and in two this assumed the proportions of megacolon. Diarrhoea was present in five cases, and had occurred in the past in twelve cases. Tetany was present in fourteen cases, and skin lesions in seven cases. Clubbing of the fingers was found in nine cases. Slit-lamp examination of the lens in thirteen cases revealed opacities in six: in no case did the opacity interfere with vision.

4. The blood picture either was normal or showed (i) hypochromic anaemia, (ii) hyperchromic megalocytic anaemia, or (iii) erythroblastic anaemia. No relation between the type and severity of the anaemia and other symptoms was established. The hyperchromic megalocytic anaemia responded to marmite. The hypochromic and erythroblastic anaemias both responded to large doses of iron.

5. Many aspects of metabolism were found to be abnormal. The blood-sugar curves after glucose were much flatter than normal. Similarly the blood urea was often below normal. In thirteen cases out of the fifteen the serum calcium was low. The plasma phosphorus was low or normal in ten cases—in the remaining five it was above the limits of normal. The height of the plasma phosphatase coincided approximately with the degree of active changes in the bones. Calcium balance estimations showed high figures for faecal output and very low figures for urinary output.

6. It is suggested that this clinical picture is dependent upon a disturbance of gastro-intestinal function resulting in deficient production, absorption, or utilization of one or more essential factors.

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APPENDICES

*Appendix A. Methods Employed**1. Haematological methods.*

The blood examinations were made at the same time each day to avoid any error from possible diurnal variations, the same pipettes being used for each case throughout the investigation. Red blood-cells were counted in a Buerker chamber. The haemoglobin was estimated by Haldane's method. Reticulocytes were counted by a wet method which gives a slightly higher count, about 1 per cent. to 2 per cent., than the ordinary dry-slide method. Equal quantities of blood and brilliant cresyl blue solution (one part saturated alcoholic solution of brilliant cresyl blue to five parts 1 per cent. sodium citrate in normal saline) were mixed on a paraffin slide and incubated in a damp chamber at 37°C. for fifteen minutes. Smears were then made in the usual way and counterstained with Jenner stain. The number of reticulocytes in 1,000 red cells was counted. The van den Bergh reaction was determined

by the method described by Beaumont and Dodds (1931), using anhydrous cobaltous sulphate as a standard. We are greatly indebted to Dr. Cecil Price-Jones for the determination of the red cell distribution curves.

2. *Methods of the metabolism ward.*

Studies of the endogenous calcium metabolism in some of our patients were carried out in a special metabolism ward under the care of an experienced sister-dietitian. The patient was given a diet containing only 100 mg. of calcium a day, but adequate in all other respects. This is necessary in order to reduce to a minimum the amount of unabsorbed calcium in the faeces. During the first few days the patient was allowed to choose whatever articles of diet seemed most attractive from the limited list of foods low in calcium (Sherman, 1926; Simmonds, 1931). Emphasis was placed upon the fact that once a diet was chosen it could not be changed during the period of study. Fluid and sodium chloride intake were kept constant, and distilled water was used in the preparation of all foods and drinks. Sufficient sodium bicarbonate was given by mouth to make the reaction of the twenty-four-hour mixed urine neutral to phenolsulphonephthalein (pH 7.3). The faeces were divided into three-day periods by the oral administration of 0.3 gm. of carmine alum lake every third day. Since constipation usually occurs on a low-calcium diet, liquid paraffin was employed as a laxative. Where carmine did not appear in the stools within twenty-four hours a simple enema made with distilled water was administered. The urine was obtained in twenty-four-hour specimens.

3. *Chemical methods.*

The calcium estimations of both food and excreta were carried out by the method of McCrudden (1910). The activity of the phosphatase in the plasma was estimated by the method of Kay (1929). In Cases 1 to 6 the inorganic phosphorus was estimated on samples collected in citrate by the methods of King (1932) and de Wesselow. In cases 7 to 15 samples were taken into oxalate and the phosphorus estimated by the method of Briggs (1924). In all cases the serum calcium was estimated by the Kramer-Tisdall method as modified by Clark and Collip (1925). The estimation of fat in the faeces was carried out by the methods of Cammidge (1914). All the chemical observations on Cases 1 to 6 were performed in the Courtauld Institute of Biochemistry, Middlesex Hospital, and we have to acknowledge our indebtedness to Professor E. C. Dodds for much personal advice and assistance.

4. *Radiographic methods.*

In estimating the density of the radiographic shadows of bones it was found necessary to use a controlled method. A control subject was chosen of the same sex, age, weight, and build as the patient. The corresponding limbs of patient and control were placed side by side and exposed simultaneously on the same negative. Where a series of radiograms was taken in one patient the same control subject was used each time.

5. *Histological methods.*

Wherever possible histological investigations of portions of bone were carried out. The methods are indicated by Professor H. M. Turnbull and Professor S. L. Baker in their reports on the corresponding cases.

Appendix B. Case Reports

Case 1. Idiopathic steatorrhoea, subacute tetany, adolescent rickets.

L. S., a boy of 16 years. (M. H. Reg. No. 2459, 1930.) Referred to authors by Dr. J. W. Brown, of Grimsby.

Clinical history. Beyond measles at the age of 3 the patient could remember no illness until at the age of 11 he developed psoriasis on the elbows, spreading to other parts of the body. At the same time he began to feel very unwell without definite symptoms. He was obliged to remain in bed and to lead the life of an invalid, and gradually became aware of 'bending of his legs'. This continued for four years until he came under the notice of Dr. J. W. Brown, who noted distension of the abdomen and that, although actual diarrhoea was not present, rather large pale motions were passed about twice a day. Enlargement of the wrists had become conspicuous during the previous two years, and the legs were increasingly deformed by genu valgum, which prevented walking. He was treated by a fat-free diet and exposure to actual and artificial sunlight.

During this time he found when writing that the hand 'suddenly became stiff, the thumb being drawn into the palm'. Cramps of the legs were frequent.

In 1930, at the age of 16, he was admitted to the Middlesex Hospital for observation. There was marked genu valgum, enlargement of the lower end of the radius on both sides (Plate 37, Fig. 8), well-marked rickety rosary; clubbing of the fingers in the form of enlargement of the nail bed, with marked antero-posterior curvature of the nails. There was evident anaemia made more conspicuous by the yellowish pigmentation of the skin which merged to brown on the knees, hands, and other areas which had been particularly exposed to the sun; in addition there were some thirty patches of psoriasis on the limbs and trunk, the largest being about the size of half-a-crown.

Abdomen was rather full and doughy on palpation; there was no fluid present; the liver and spleen were not palpable. Chvostek sign positive. Trousseau sign negative.

Special examinations. *Eyes:* right lens showed faint spot of opacity in the centre near the posterior capsule, and a few thin, hairlike, spoky opacities in the periphery; left lens showed only a few fine, peripheral, spoky opacities. (Mr. Affleck Greeves.) *Radiograms of bones:* typical rickety appearances at lower ends of radii (Plate 40, Fig. 12); general osteoporosis; pituitary fossa normal. *Colon:* the lumen moderately increased in size, especially in pelvic portion.

<i>Blood counts.</i>	14.8.30	18.10.30
Hb.	75	74
Reds	3,900,000	4,900,000
Whites	8,000	9,000
Polymorphs	56	48
Lymphocytes	35	44
Large mononuclears	6	6
Eosinophils	3	2
		few poikilocytes no nucleated reds.

Urine: concentration 1,010 to 1,025; faint trace of albumin: diastase 33 units. *Wassermann reaction:* negative. *Fractional gastric analysis:* free HCl and total acidity within normal limits.

Glucose tolerance: blood-sugar 102, 105, and 104 mg. per 100 c.c. at half-hour intervals after 50 grm. glucose by mouth. *Van den Bergh reaction*: faint direct positive. *Fouchet's reaction*: positive. *Plasma phosphatase*: 1.06 mg. *Blood analysis*: N.P.N. 24 mg. per 100 c.c., urea 19 mg. per 100 c.c. (average of four observations), serum Ca 7.9 to 8.9 mg. per 100 c.c. (five observations), plasma P. 5.3, 6.3 mg. per 100 c.c., cholesterol 117, 132 mg. per 100 c.c.

Faeces.

	27.8.30	6.9.30	29.1.31
Total fat	63.9	52.4	30.7
Unsoaped	30.8	24.8	12.9
Neutral	2.9	10.1	1.7
Free fatty acid	27.9	14.7	11.2
Combined fatty acid	33.1	27.6	17.8

(the last readings were whilst patient was on very low-fat diet)

Progress. Patient was given calcium lactate gr. 120 daily with radiostol 6 tablets daily (18,000 international units of irradiated ergosterol) and Bland's pill gr. 30 daily. Low-fat diet. Double osteotomy of lower ends of femora performed by Mr. Blundell Bankart. Good healing. Patient walking well on discharge and feeling better in general health. Mild anaemia still present; Chvostek sign still positive.

Case 2. Idiopathic steatorrhoea, erythroblastic anaemia, adolescent rickets.

B. B., a man of 26 years. (M.H. Reg. No. 5103, 1931; L.H. Reg. No. 31997, 1931.) Referred to authors by Mr. L. Paton.

Clinical history. Born in Surrey. The patient's mother says that he had frequently to be taken to hospitals on account of rickets as a baby; he had mumps and measles whilst at school.

At the age of 14 he began to work, but after several years had to stop on account of 'gastric influenza' followed by a disease characterized by distension of the belly, some abdominal pains with much gurgling, and diarrhoea with pale motions; there was no fever. For this he was kept in bed at home for six months, and was then in hospital for several months. His legs became weak, and he could not get about except with the aid of a stick. Legs began to bend. During subsequent years he had several relapses, abdominal distension, pain, and diarrhoea; he gradually became more incapacitated until walking was impossible on account of genu valgum.

In 1925 he began to have a cough with the expectoration of mucus but not blood. He was treated as an out-patient at a chest hospital and sent to a sanatorium. The tubercle bacillus has not been found in the sputum.

In May 1930, he fell and hurt his shoulder, the clavicle being fractured, although it rapidly united with somewhat extensive callus formation. Three months later he was admitted to the R. N. Orthopaedic Hospital for treatment of the deformities and was transferred to the Middlesex Hospital for observation.

On admission he was found to be markedly infantile in type, not only having the physical appearance of a boy of 14, but having an unbroken voice and general mental characteristics corresponding to his apparent rather than his actual age. He began to shave at 23 and now only does so twice a week. There was a diffuse psoriatic rash on the limbs (Plate 36, Fig. 5) and trunk pronounced by Drs. MacCormac and Parkes Weber to be seborrhoeic psoriasis; marked genu valgum; the tongue was somewhat large and its epithelium atrophic. The patient appeared very anaemic; there was marked

enlargement of the lower radial epiphyses; the nails showed swelling at the nail bed with a vertical antero-posterior curvature of the nails (Plate 36, Fig. 5). The abdomen was protuberant and doughy to palpation. The costochondral junctions were prominent. Chvostek sign positive. Trousseau sign negative. *Eyes*: right lens showed one faint radial streak in anterior cortex above; no other lens opacity. Left lens showed one small vacuole in anterior cortex and a few microscopic dots in other parts of the lens. (Mr. Affleck Greeves.)

Special examinations. Radiograms of bones: failure of union of epiphyses most marked at lower ends of radii; epiphyseal lines irregular and much increased in width; general osteoporosis of considerable degree. *Colon*: moderate but quite definite dilatation. *Chest*: increased density at base of right lung and suggestion of bronchiectasis with cavity. *Wassermann reaction*: negative.

21.12.31. Blood Count

Erythrocytes	3,600,000 per c.mm.
Haemoglobin 40 per cent.
Colour index	0.55
Leucocytes	6,400 per c.mm.
Polymorphs 50 per cent.
Lymphocytes 46 " "
Large mononuclears 3 " "
Basophils 1 " "

284 nucleated red cells per 100 white cells—only nine of these show slight immaturity of the nucleus. The rest have small pyknotic nuclei.

Reticulocytes 0.5 per cent.

Anisocytosis and poikilocytosis—many of the cells appear torn and much deformed in shape.

Van den Bergh reaction, indirect 0.5 units.

Price-Jones curve, Mean diameter 7.6595 μ

(within normal limits)

Variability 15.19 per cent.

Microcytosis 3.6 " "

Megalocytosis 23.2 " "

Many cells are mere rings: 122 in 500 are full coloured.

Urine: concentration 1,008 to 1,017, faint trace albumin. Gastric analysis refused. *Blood analysis*: blood-sugar: (fasting) 104 mg. per 100 c.c. N.P.N. 17 to 23 mg. per 100 c.c. Blood urea 23 mg. per 100 c.c. Serum calcium 7.1 to 9.4 mg. per 100 c.c. Plasma phosphorus 3.4 to 5.2 mg. per 100 c.c. Plasma phosphatase 0.599 mg. *Stools*: total fat, 50 to 56 per cent.; unsoaped fat, 19 to 21 per cent.; neutral fat, 7 to 8 per cent.; free fatty acid, 12 to 16 per cent.; combined fatty acid, 29 to 36 per cent. (in a large series). *Calcium balance*: the calcium output was estimated in the urine and faeces for three three-day periods (Fig. 22). The patient was kept on a weighed diet of known low-calcium content (0.38 gm.). The calcium output in the urine was 0.03 gm.: that in the faeces was 0.56 gm.

Progress. After three months' treatment with low-fat diet together with calcium lactate gr. 120 and radiostol 5 tablets daily (15,000 international units), the patient was re-transferred to R.N. Orthopaedic Hospital. Double osteotomy of femora by Mr. L. Paton; the bone was soft and could be readily cut with a knife.

He sometimes complained of cramps in his legs, saying that the feet seemed to tighten up as soon as he walked. Later he was transferred to the London Hospital for further haematological investigations as, although walking was good, anaemia was worse.

There was no response to marmite, but when 90 grains of Bland's pill were given daily there was rapid clinical and haematological improvement. The haemoglobin rose from 40 per cent. to 98 per cent. in fourteen weeks. Considerable anisocytosis and as many as 186 nucleated red cells per c.mm. were still present, however, in stained films.

Pathological Report. (Professor S. L. Baker.) Tissue removed at operation (13.6.32).

Portion of bone from lower end of femur.

The bone is soft and easily cut with a knife. It was fixed in 10 per cent. formol saline; portions were then placed in Müller's fluid. Another portion was embedded in paraffin without decalcification and it was found possible to cut sections of this, though with difficulty. After seven days in Müller's fluid fairly good paraffin sections were obtainable. In sections stained with Weigert's iron-haematoxylin and eosin there was no appreciable difference in staining reactions between the undecalcified and the Müller sections; the following description therefore applies to both of these.

The sections include part of the periosteal layer, and the subjacent trabecular bone to a depth of about 1.5 cm.

The cortical zone is occupied by coarsely trabecular bone showing considerable sized marrow spaces filled with blood-forming marrow. Scattered small Haversian systems are seen in the thicker trabeculae. The architecture of the trabeculae is complex, each consisting of a fragmentary mosaic of osseous systems showing very variable haematoxylin staining. A few of these systems show a well-marked blue staining, perhaps equal to that of fully calcified bone, but the majority show either a marked diminution in density or do not stain at all with haematoxylin.

The bone has a well-formed lamellar structure and the fragments of the various systems which compose the trabeculae stand out in contrast to one another by reason of (1) the directional plane of their lamellae; (2) sharply defined, irregular, sometimes definitely lacunar, haematoxyphil borders; (3) variations in the intensity of haematoxylin staining of contiguous systems.

The non-calcified bone (osteoid) is seen to be located for the most part to the more superficial portions of trabeculae or around Haversian spaces. The width of the non-calcified zones on the surface ranges from 5-16 lamellae and Haversian systems composed of about 10 lamellae may be completely non-calcified. Although variations in calcification usually correspond to different lamellar systems it is not uncommon for the same system of lamellae to vary in haematoxylin staining from place to place, in which case there is a gradual colour transition from blue to pink.

There is little evidence of osteoclastic activity, the trabeculae being covered by lamellar osteoid tissue on the surface of which is a single layer of spindle-shaped osteoblasts; no osteoclasts were seen. It is only in the older osseous systems within the trabeculae that the lacunae of an earlier bone resorption can be seen. The marrow spaces are for the most part well filled with blood-forming cells, but at a few spots a layer of spindle cells without blood-forming elements covers portion of a trabecula.

Conclusion. There has been a disturbance of calcification which has affected practically all the bony tissue in the sections. It is possible that some of the oldest systems in the trabeculae may contain a normal amount of calcium, but the remainder show various grades of failure of calcification, and much of the more recently deposited bone, although it has a well-formed regular lamellar structure, is completely non-calcified.

The very numerous and irregular osseous systems which make up the individual trabeculae indicate much alternating resorption and deposition in the past.
(S. L. B.)

Case 3. Idiopathic steatorrhoea masked by megacolon, latent tetany, hypochromic anaemia, osteomalacia.

B. B., a girl of 17 years. (M. H. Reg. No. 7581, 1931.) Referred to authors by Mr. E. P. Brockman.

Clinical history. Patient was a healthy baby until twelve months old. At fourteen months she cut her double teeth, which seemed all right, but she had diarrhoea and vomiting for fourteen days, after which time she regurgitated her food and began to waste. She attended a babies' clinic for twelve months, and was kept on milk and water and Liebig's extract. Stools were always offensive and unformed, belly very distended, front teeth rapidly decaying. At the age of two years patient could sit up but did not crawl; she bent her left humerus one night in bed. Aged $2\frac{1}{2}$ years admitted to Waterloo Hospital for six weeks without relief.

At the age of 3, convalescent home for a long period and was retransferred to Waterloo Hospital. On discharge attended as out-patient for five years, and at age of seven began to walk in irons. Slow gain of weight; motions always pale, never formed, full of curds. Was given much fat and cod liver oil by medical orders. Diagnosis at this time was rickets and possibly tuberculous peritonitis. There was no fever. At a later date the diagnosis was distension of the small and large intestines, possibly due to tuberculous peritonitis. When second teeth appeared they rapidly decayed.

In 1927, aged 14, was in St. Thomas's Hospital for over a year, and was subsequently readmitted in 1929 with periods at convalescent homes between. Deformity of legs had been more and more pronounced since early childhood, and in St. Thomas's Hospital osteotomies were performed, after which she could walk well, but her legs rapidly bent once more.

In September 1930, aged 17, whilst on holiday fell and broke her leg; admitted to cottage hospital and put in plaster, subsequently admitted to convalescent home and transferred to the Middlesex Hospital.

On admission there were marked deformities of limbs, there being hyper-extension at elbows and wrists with enlargement of radial epiphyses. There was marked outward and forward bending of femora and extreme backward bending at lower ends, triple displacement of both knees being present with extreme hypermotility (Plate 37, Fig. 6). The right femur was now united, but still in plaster. The circumference of the thorax was much greater at the bottom than at the top, 26 inches above nipples, 30 inches at the lower margin of sternum, $24\frac{1}{2}$ inches at umbilicus. The right hypochondrium was hyper-resonant, liver dullness being unobtainable. Enlargement of costochondral junctions. Antero-posterior curvature of nails. Obvious anaemia, peach-like complexion, white in shaded areas, tanned in exposed areas. Tongue normal. Chvostek sign positive. Trousseau sign negative. Patient infantile in stature, her sitting height being $26\frac{1}{2}$ inches against a normal of $33\frac{1}{2}$ inches. Breasts scarcely prominent at all. Menstruation began in hospital at age of 18.

Special examinations. *Eyes*; there were a few fine peripheral spoky opacities in both lenses; centres clear (Mr. Affleck Greeves). *Radiograms of bones*: very marked generalized osteoporosis with many transverse lines and failure of union of epiphyses. *Colon*: megacolon with many redundant loops; seven pints of barium sulphate insufficient to distend the large intestine fully (Plate 42, Fig. 16).

Haematological. On admission: red cells, 5,100,000 per c.mm., Hb. 72 per cent., white cells, 10,200 per c.mm. Normal differential count. Slight anisocytosis and poikilocytosis. 15.3.32. Red cells, 4,000,000 per c.mm.; Hb. 60 per cent.; C. I., 0.75; white cells, 3,700 per c.mm.; polymorphs, 60 per c.mm.; lymphocytes, 34.5 per cent.; large mononuclears, 4.5 per cent.; eosinophils, 1 per cent.; reticulocytes, 1.7 per cent.; anisocytosis with a few definite megalocytes. Polychromasia slight, but considerable variation in density of staining of red cells. Platelets scanty. Van den Bergh reaction indirect, 0.45 units; mean diameter, 7.578 μ ; variability, 10.2 per cent.; megalocytosis, 5.6 per cent.; 237 deep stained cells showing mean diameter, 7.881 μ ; 263 pale cells showing mean diameter, 7.305 μ . *Urine*: concentration 1,008 to 1,016. It was impossible to secure higher concentration by urea administration. A faint trace of albumin occasionally present, no casts, blood-pressure never raised, blood urea and N.P.N. constantly very low. *Wassermann reaction*: negative. *Gastric analysis*: normal curve of HCl and total acidity. *Glucose tolerance*: blood-sugar 71, 70, 71, 74, and 70 mg. per 100 c.c. at intervals of 30 minutes after administration of 50 gm. glucose. *Blood analysis*: N.P.N. 17 to 22 mg. per 100 c.c. Blood urea 14 to 20 mg. per 100 c.c. Serum calcium 7.2 to 8.6 mg. per 100 c.c. Plasma phosphorus 2.7 to 4.6 mg. per 100 c.c. Cholesterol 121 to 140 mg. per 100 c.c. (These figures are high and low averages of twenty-four observations made at weekly intervals.) *Stools*: total fat, 55 to 67 per cent.; unsoaped fat, 14 to 23 per cent.; neutral fat, 3.5 to 6.5 per cent.; free fatty acid, 13 to 25 per cent.; combined fatty acid, 23 to 44 per cent. (The above are high and low averages of sixteen observations made at intervals.)

Progress. The patient was kept on a low-fat diet with full doses of irradiated ergosterol, calcium lactate, and calcium gluconate. It was found impossible to abolish the Chvostek sign by any of these means, nor was this result obtained when daily intramuscular injections of calcium gluconate and laevulinate were added, together with ultra-violet irradiation. On treatment with large doses of iron the haemoglobin rose to 74 per cent. A month after discharge from the Middlesex Hospital the patient broke her leg and was admitted to St. Thomas's Hospital, where plaster was put on. She is now at home and remains under observation. Her mother states that she is evidently better because her bones now break, whereas formerly they only bent.

Case 4. Idiopathic steatorrhoea, adolescent rickets.

L. D., a girl of 15 years. (R.N. Orthopaedic Hospital, Country Branch, 1931.) Referred to authors by Mr. Laming Evans.

Clinical history. Admitted to the Hospital for Sick Children, Great Ormond Street, in 1921, at the age of 5, for diarrhoea and cessation of growth during the previous eighteen months.

X-ray examination showed no rarefaction of the long bones; blood urea 30; the stools contained much fat, which was well split; she was sent to a hospital at Torquay for three years.

In 1927, at the age of 11, she was an in-patient for over three months at the Queen's Hospital for Children, Hackney. There was much diarrhoea and vomiting with enlargement of the abdomen. Infantilism was noted; osteoporosis of both femora. *Stools*: fatty, total fat, 45.3 per cent.; neutral fat, 24 per cent.; fatty acid, 21.3 per cent. Serum calcium, 8.4 mg. per 100 c.c.; plasma phosphorus, 5.0 mg. per 100 c.c.

In 1931, at the age of 15, on admission to the Orthopaedic Hospital, Stanmore: definite infantilism, height 3 feet 1½ inches; had never menstruated; 12 inches of genu valgum all in the femora.

She was a pale, under-sized child appearing ten years old. Tongue furred; teeth poor, with many stumps.

Cardiovascular system normal; lungs normal; no gross deformity of thoracic wall except that subcostal angle was wide and costochondral junctions enlarged. *Abdomen*: protuberant and soft; liver and spleen not palpable. *Limbs*: upper, enlargement of lower radial epiphyses; lower, hips normal, knees, extreme genu valgum, feet in valgus on standing. Spine, straight. Definite antero-posterior curvature of nails. Chvostek and Trousseau signs negative.

Special examinations. X-ray examination: definite osteoporosis; failure of union of epiphyses and other changes typical of rickets.

Haematological. Red cells, 5,008,000 per c.mm.; Hb., 82 per cent.; white cells, 17,000 per c.mm.; polymorphs, 50 per cent.; lymphocytes, 48 per cent.; large mononuclears, 42 per cent. *Urine*: no abnormality. *Wassermann reaction*: negative. *Glucose tolerance*: blood-sugar, 105, 125, 160, 140, and 80 mg. per 100 c.c. at intervals of 30 minutes after 50 grm. glucose. *Gastric analysis*: a high normal curve for HCl reaching 70 at three-quarters of an hour and falling to 20 when the stomach was empty at 1½ hours. *Blood analysis*: N.P.N. 25 mg. per 100 c.c.; blood urea, 22 mg. per 100 c.c.; serum calcium, 9.8 mg. per 100 c.c.; plasma phosphorus, 5.5 mg. per 100 c.c. *Stools*: total fat, 50.7 per cent.; unsoaped fat, 31.6 per cent.; neutral fat, 4.7 per cent.; free fatty acid, 26.9 per cent.; combined fatty acid, 19.1 per cent. (Other analyses similar but somewhat lower on fat-free diet.)

Progress. After three months' treatment with sunlight and full doses of calcium salts and irradiated ergosterol, double osteotomy with removal of small wedge of bone was performed. Bruising beneath the tourniquet in each leg very marked. Bones united well; patient returned home in apparently good health six weeks after operation.

Pathological Report. (Professor S. L. Baker.) Tissue removed at operation (13.6.32)

Portion of bone from lower end of femur.

The section is completely decalcified; it is therefore impossible to make any certain statement as to amount of calcification.

A growing epiphysis is included in one of the sections. Here the cartilage cells are normally and regularly arranged and the formation of lamellar bone upon the cores of cartilage is proceeding in an orderly manner without any formation of irregular osteoid tissue. From this I should judge that the provisional calcification of the cartilage and the subsequent deposition of bone were proceeding in the normal manner. Active osteoclastic erosion is proceeding both at the junction of bone and cartilage and in the

subperiosteal bone. As far as can be judged this is not in excess of the normal process of bone erosion. (S. L. B.)

Case 5. Idiopathic steatorrhoea, infantilism, osteomalacia.

F. D., a widow of 58 years. (M. H. Reg. No. 21118, 1931.) Referred to authors by Dr. H. Joules, of Birmingham.

Clinical history. No information as to birth or early feeding. Healthy until 16 months old. Bad fall at 16 months; no injury of bones, but rickets was then first noticed.

Aged 3½ years, typhoid fever.

Aged 4 years, 'dysentery', severe diarrhoea with weakness.

Aged 5 years, 'consumptive bowels', incontinence of faeces with wasting; this illness lasted until the age of twelve years. She remembers that diarrhoea was so chronic that she used to pass days seated cross-legged on a lavatory seat. Her teeth became carious at the age of 10 and had all disappeared by 20.

By 12 years old the patient was able to stand. She attended school for two years at 15; she then had some bowing of the legs, but less than she has now.

Menstruation began at the age of 21.

At 34 the patient married, contrary to advice; at this time she experienced some loss of function in her arms and hands with a sensation of pins and needles.

At 36 she miscarried, when 3½ months pregnant, and was very ill, an illness from which she has never recovered. The patient frequently had attacks of 'ulcerated stomach', of which vomiting and diarrhoea were the principal symptoms. She was also subject to rheumatism in the hands.

Between 39 and 40 she developed a severe cough; her weight was then 6½ stone. It was at this time that curvature of the spine first became apparent.

About the age of 40 she had shooting pains in both legs below the knee; she was very weak, and the earlier deformities became more pronounced.

The menopause occurred at 46.

When she was 54 her husband died and she was left with ten shillings per week, five shillings of which went in rent. After living for five months in a dark and airless room, which she rarely left for more than a quarter of an hour per day, her recent illness began. For the last eighteen months the patient has suffered from vomiting and anorexia, loss of weight, inability to walk owing to weakness, pain in long bones, and increasing deformity. She has had attacks of spasm of the hands and has become very nervous. For the last twenty years she has had difficulty in writing owing to 'drawing up of the fingers'. She bruises very easily.

In June 1930 she was admitted to Selly Oak Hospital.

Her condition at that time was: height 4 ft. 4½ in.; weight 3 st. 12½ lb.; extremely emaciated; unable to stand or sit owing to pain in legs and spine. Very marked tenderness was found over all the bones of the body. A kyphoscoliosis of the whole dorsal spine was present, there was severe radial bowing of the bones of the forearm, extreme forward curvature of the lower third of the femora. The tibiae were bowed backward and inward, especially in the upper third; the pubis was much flattened.

Interspinous	10¾ in.
Intercristal	11¼ in.
External conjugate	6½ in.

There was anterior beaking; the vagina admitted one finger only. The calvaria showed bossing of the parietal bones. Nothing abnormal in circulatory or respiratory systems. Clubbing of fingers. Trousseau and Chvostek signs negative. *Alimentary system*: edentulous; abdomen protuberant and doughy; liver and spleen not palpable.

Progress. The patient was treated with real and artificial sunlight, radiostol and calcium lactate by the mouth, and was placed on a high-calcium diet. She responded well. In October 1930 the patient was discharged and returned to her old home conditions. In seven weeks her symptoms returned; she was readmitted in December 1930. X-rays at this time showed the deformities described and a diffuse osteoporosis. The patient once again responded well to the treatment, her pains disappearing in five days.

In the middle of September, 1931, the patient was transferred to the Middlesex Hospital. She then weighed 4 st. 9½ lbs. (Plate 35, Fig. 1); apart from this increase in weight, her physical condition was as described above. Diarrhoea was never present in spite of high-fat percentage in stools. There was slight xanthoma on upper part of abdomen.

Further investigations were carried out while in hospital, and treatment was given on the same lines as at Birmingham, with the addition of massage to the legs.

Special examinations. *Radiograms of bones*: all the bones show decrease in calcification, there is gross deformity of the pelvis (Plate 38, Fig. 9) and bowing of the femora and tibiae; these bones show sparse but heavily-lined trabeculation at the ends; in the shafts they show irregular calcification during growth. The thorax shows deformity of the ribs in the anterior axillary line. The skull shows thickening of the cranial vault with dense bone. The pineal body is calcified.

Barium enema. The enema flowed freely and, in all, five pints were given. The sigmoid loop was long, redundant, and distended. The descending colon and splenic flexure were also redundant and distended, showing no haustration. After four pints had been administered the enema was only just passing the splenic flexure. On emptying, the barium sulphate was freely evacuated. The proximal colon appeared fairly normal and not distended.

Haematological. Red cells, 4,000,000 per c.mm.; Hb., 85 per cent.; leucocytes, 7,000 per c.mm.; C.I., 1.0; differential,—polymorphs, 50 per cent.; lymphocytes, 42 per cent.; large mononuclears, 4 per cent.; eosinophils, 2 per cent.; mast cells, 2 per cent. Three normoblasts per 100 leucocytes. *Urine*: no abnormality. Concentrated well. *Wassermann reaction*: negative. *Gastric analysis*: hypochlorhydria, free HCl 16, 8, 10, 10 at ¾ to 1½ hours after meal. *Glucose tolerance*: blood-sugar, 94, 135, 165, 135, and 125 mg. per 100 c.c. at intervals of 30 minutes after 50 gm. glucose. *Blood analysis*: N.P.N., 15 to 19 mg. per 100 c.c.; blood urea, 15 to 28 mg. per 100 c.c.; serum calcium, 8.5 to 9.5 mg. per 100 c.c.; plasma phosphorus, 2.2 to 5.9 mg. per 100 c.c.; cholesterol, 135 to 165 mg. per 100 c.c. (average of a series.) *Stools*: total fat, 42 to 64 per cent.; unsoaped fat, 22 to 39 per cent.; neutral fat, 4.9 to 22 per cent.; free fatty acid, 13.5 to 17 per cent.; combined fatty acid, 24 to 38 per cent. (average of a large series).

Progress. The patient was afebrile all the time she was in hospital, and was discharged after three months, having gained 5 lbs. in weight. The bone pains rapidly improved on a low-fat diet and full doses of calcium and irradiated ergosterol.

Case 6. Idiopathic steatorrhoea, latent tetany, erythroblastic anaemia, deformity of skull, infantilism, rickets.

R. J., a man of 34 years. (M.H. Reg. No. 26865, 1932.) Referred to authors by Drs. J. B. Davey and J. F. Lidderdale, of Cheltenham.

Clinical history. In infancy patient was a delicate child. His mother abandoned him when nine months old and he was adopted; at about this time his arm was broken; he was a very thin baby and had constant bowel and stomach trouble; walked late; was always intelligent, but missed much of his schooling owing to illness, which took the form of recurrent attacks of diarrhoea. His growth was always impaired and he had a conspicuously bad colour during childhood. At puberty his development underwent little change and his final height is 4 ft. 9 in. His father was a short man, about 5 ft. 3 in.

From babyhood to twenty-seven years of age he had periodic attacks of severe diarrhoea and occasional vomiting, but after this his condition improved, the gastro-intestinal symptoms disappearing. In December 1931 there was a severe recurrence of diarrhoea with very light stools, which continued and led to his admission to Cheltenham Hospital, under the care of Dr. J. F. Lidderdale. He had never had any abdominal pain. On admission to Cheltenham Hospital he was put on a low-fat diet, and his severe anaemia, the peculiar nature of which was noted by the physician in charge, was treated with liver, iron, and pig's stomach. Achlorhydria was noted. Diarrhoea improved greatly. Anaemia responded well to large doses of iron. His weight rose from 5 st. 2 lb. to 6 st. 1 lb.; patient felt better than he had done for years. He was admitted to the Middlesex Hospital, in February 1932.

Condition on admission: Infantilism was marked, but his true height was really greater than the recorded height because considerable bowing of both femora and genu varum contributed to his shortness. The calvaria was notably large and the malar bones prominent, producing a peculiar semi-mongolian facies; the whole shape of the head was very striking, suggesting an equilateral triangle standing on its apex (Plate 39, Fig. 11A). The chest was somewhat barrel-shaped; Harrison's sulcus well marked, with some beading of the costochondral junctions. Abdomen somewhat protuberant and inclined to be pendulous when the patient was standing. No abnormality found on palpation. Cardiovascular, pulmonary, nervous, and urinary systems normal, but Chvostek sign faintly positive, Trousseau sign negative.

Antero-posterior curvature of finger and toe nails. Mouth edentulous, all teeth having been removed for gross sepsis six months previously. Mucous membrane of the tongue atrophic.

Special examinations. *Eyes:* disseminated choroiditis present, indistinguishable from that frequently seen in congenital syphilis; no opacities in lenses. (Mr. Affleck Greeves.) *Wassermann reaction:* negative. *X-ray examinations.* *Bones:* epiphyseal lines still visible, suggesting late union; some splaying of lower ends of the bones towards wrist joints. Definite osteoporosis compared with control. Considerable thickening of bones of calvaria with small areas of increased density on both sides of the frontal and parietal bones (Plate 39, Fig. 11B).

Barium enema: colon showed considerable dilatation, greatest in descending portion; four pints of barium sulphate taken with ease.

Haematological. When first seen at Cheltenham, Dr. J. B. Davey noted Hb. 34-40 per cent.; red cells, $3\frac{1}{2}$ - $4\frac{1}{2}$ million per c.mm.; C. I., 0.4-0.5; white cells,

6-9 thousand per c.mm.; normal differential, very large numbers of normoblasts, sometimes as many as 173 to 100 leucocytes; very great anisocytosis with many microcytes, and at times numerous macrocytes; 'the whole picture is very curious; leucopenia with very marked neutropenia, enormous numbers of normoblasts and a tendency to macrocytosis with low colour index and fairly severe anaemia'. Anaemia greatly improved by treatment at Cheltenham; in London Hb. was 70 per cent.; red cells, $4\frac{1}{2}$ -5 million per c.mm.; mean diameter, 8.0965μ ; variability, 10.6 per cent.; megalocytosis, 33.8 per cent.; microcytosis, 0.4 per cent.; 75 deep-stained cells, 425 pale cells. C.I. 0.7; white cells, 6-8 thousand per c.mm.; polynuclear neutrophils, 26 per cent.; polynuclear eosinophils, 11 per cent.; lymphocytes, 59.5 per cent.; large mononuclears, 1 per cent.; basophils, 2.5 per cent.; reticulocytes, 0.6 per cent.; nucleated reds, 29 per 200; leucocytes, 899 per c.mm. Anisocytosis with megalocytes and microcytes; one of twenty-nine nucleated reds showed slight structure in the nucleus. The others were all small pyknotic nuclei. *Urine*: nothing abnormal. *Gastric analysis*: complete achlorhydria with low total acidity. *Glucose tolerance*: blood-sugar 85, 100, 100, 110, and 115 mg. per 100 c.c. at half-hour intervals after 50 grm. glucose. *Blood analysis*: N. P. N. 24 to 28 mg. per 100 c.c.; blood urea, 21 to 23 mg. per 100 c.c.; serum calcium, 8.8 to 9.2 mg. per 100 c.c.; plasma phosphorus, 4.3 mg. per 100 c.c.; cholesterol, 200 mg. per 100 c.c. *Stools*: total fat, 60 per cent.; unsoaped fat, 50 per cent.; neutral fat, 38 per cent.; free fatty acid, 8.8 per cent.; combined fatty acid, 9.5 per cent. (averages of large series).

Progress. The patient returned home to work in apparently good health; he continues to take a very low-fat diet with calcium, iron, and liver extract.

Case 7. (Vaughan and Hunter, 1932.) Idiopathic steatorrhoea, tetany, megalocytic hyperchromic anaemia.

N. B., a single woman of 22 years. (L.H. Reg. No. 40652, 1932). Referred to authors by Dr. D. S. Campbell, of Grimsby.

Clinical history. She was born in Grimsby, was an only child, and since babyhood had always had loose stools. They were pale, but not bulky or offensive, and never contained blood or mucus. She was not backward as a child, was at school until the age of 17, but never had the energy to play games. She remembers some time at the end of her school training having had attacks, when she lost the use of the fingers because of numbness. Five years ago she went to Switzerland, feeling quite well, and after two weeks she had a severe attack of diarrhoea lasting six weeks. She was in bed for two months, and on getting up had attacks of spasms in the hands. Three years ago she began having attacks of diarrhoea every two weeks. The condition was relatively painless, and she passed as many as eight motions a day, more in the morning than in the evening. About this time she had tinglings and numbness in the fingers, and in some attacks the thumb became stiff and tucked into the palm. Sometimes the feet and legs were stiff, and the face twitched. The tetany sometimes occurred when no diarrhoea was present. For intervals up to six weeks she would be free from all symptoms. In August 1929, her case was investigated by Dr. Stanley E. Denyer, of Hull. He thought that her symptoms were associated with calcium deficiency, and therefore treated her with injections of calcium compounds together with a diet containing large quantities of milk. He then referred her to Dr. Seton Montgomery, who reported as follows: 'A controlled radiogram of the right hand showed a slight uniform diminution of

calcification.' During 1930 attacks of diarrhoea and of tetany completely interfered with her study of music, especially playing the piano. Catamenia commenced at 14, and have been normal since. She has never broken a bone, and there is no history of bone disease in the family.

Clinical examination (May 6, 1931). Weight 7 st. 4 lb.; height 5 ft. 1 in. Pale skin and mucous membranes, slight malar flush. No skin eruption, no abnormality of nails or hair. *Teeth*: a large number of fillings. *Eyes*: slit-lamp examination of the lenses showed no abnormality. Small adenoma 2 cm. diameter, in isthmus of thyroid. Chvostek sign negative. Trousseau sign positive. No bone deformity. Heart and lungs normal. Blood-pressure 130/90. Moderate distension of abdomen, no tenderness.

Special examinations. *Urine*: normal; no Bence Jones protein present. *Stools*: pale, porridgy; total fat, 47.1 per cent.; unsoaped fat, 16.5 per cent.; neutral fat, 6.8 per cent.; free fatty acid, 9.7 per cent.; combined fatty acid, 30.6 per cent.; no occult blood. Test meal: free HCl, 0.16 per cent.; total acidity, 66. Serum calcium, 7.9 mg. per 100 c.c. Plasma phosphorus, 2.5 mg. per 100 c.c. Plasma phosphatase 0.305 mg. *Calcium balance*: the calcium output was estimated in the urine and faeces for three three-day periods (Fig. 22). The patient was kept on a weighed diet of known low-calcium content (0.31 grm.). The calcium output in the urine was 0.03 grm.; that in the faeces was 0.14 grm. *Radiograms of bones*: controlled radiograms of bones showed undoubted diminution of calcification with wide-meshed spongiosa in the lower end of the radius and the carpal bones. Corticaes of metacarpals, tibia, and fibula, identical with normal control. Corticalis of right radius thinner than in control, but in no place trabeculated. Union of epiphyses normal throughout all radiograms taken. Examination by opaque enema showed the lumen of the colon to be normal. Radiograms of the kidneys and urinary tract were normal. *Blood count*: red blood-cells, 2,500,000 per c.mm.; haemoglobin, 55 per cent.; colour index, 1.1; white blood-cells, 4,400 per c.mm.; polymorphs, 30 per cent.; lymphocytes, 66 per cent.; eosinophils, 1 per cent.; large mononuclears, 3 per cent. *Wassermann reaction*: negative.

Progress. She was given a low-fat, high-calcium diet, with the addition of calcium lactate (10 grm.) and 6,000 international units of irradiated ergosterol daily. There was immediate improvement of the diarrhoea, and she began to pass only two stools a day. The tetany disappeared. Iron in large doses was given, but the anaemia remained unaltered for six months.

On December 29, 1931, she was admitted to a nursing home for intensive treatment of the anaemia.

Clinical examination. Weight 6 st. 13 lb. Pale skin with malar flush and slight icteric tinge of conjunctivae. Tongue, raw with red edges. (To a direct question she answered that her tongue had often been sore.)

Special examinations. *Stools*: total fat, 18.7 per cent.; unsoaped fat, 11.8 per cent. *Sugar-tolerance test*: fasting blood-sugar, 0.054 per cent.; blood-sugar after 50 grm. glucose by mouth—in 40 minutes 0.076 per cent., in 80 minutes 0.075 per cent., in two hours 0.083 per cent. No glycosuria throughout. Serum calcium, 9.7 mg. per 100 c.c. Plasma phosphorus, 3.5 mg. per 100 c.c. Plasma phosphatase, 0.182 mg. Blood urea, 0.018 per cent. *Blood count*: red blood-cells, 2,500,000 per c.mm.; haemoglobin, 52 per cent.; colour-index, 1.04; white blood-cells, 2,400 per c.mm.; polymorphs, 39 per cent.; lymphocytes, 58 per cent.; eosinophils, 1 per cent.;

large mononuclears, 2 per cent.; reticulocytes, 1.7 per cent.; platelets scanty, great anisocytosis, no poikilocytosis. The mean diameter of the red blood-cells was 8.115μ , the variability 11.7 per cent., and there was a megalocytosis of 37.2 per cent. giving a curve compatible with a diagnosis of pernicious anaemia. The indirect van den Bergh reaction was 0.75 van den Bergh units.

Progress. In order to simplify the conditions of the experiment as far as possible, during the initial period the patient was given no red meat and no fresh fruit or green vegetables. Chicken once a day was allowed. To this was added 12 grm. of marmite, usually taken cold. This was much disliked at first, but was soon tolerated. Daily blood observations were made. The reticulocytes started to rise on the sixth day, reaching a maximum of 17.2 per cent. on the eleventh day, and then falling slowly to normal. This was followed by a rapid rise in both red blood-cells and haemoglobin. Thirty-nine days later the red blood-cells were 4,000,000 per c.mm.; haemoglobin 78 per cent.; colour index, 0.9. The indirect van den Bergh reaction was 0.2 van den Bergh units. Progress has continued, and the red blood-cells are now 5,200,000 per c.mm.; haemoglobin, 88 per cent.; colour index, 0.84. There is still a leucopenia, the white blood-cells being constantly between 2,000 and 3,000 per c.mm. The striking haematological improvement was accompanied by an increased sense of well-being, and by a gain in weight—1 st. 3 lb. in ten weeks, in spite of occasional attacks of diarrhoea lasting one to two days.

Case 8. (Vaughan and Hunter, 1932.) Idiopathic steatorrhoea, tetany, megalocytic hyperchromic anaemia, pellagra-like skin eruption.

M. W., a married woman of 40 years. (L.H. Reg. No. 40997, 1930.) Referred to authors by Dr. W. M. Fairlie.

Clinical history. She was born in London. All her life she has had attacks of diarrhoea with yellow offensive motions and intervals of relative freedom. She improved when she was 7 years old, but became worse after her only child was born, eleven years ago. The attacks last about five days, when she passes about six stools a day, and many more at night. Between attacks the bowels are open three times daily, and she may have to get up four times at night. She lost weight in attacks, but preserved an excellent appetite. There was no history of bone disease in the family, neither did she ever break a bone. Catamenia started at the age of 16 years, and remained regular until February 1930. She first noticed cramps in the hands and feet in June 1930.

On February 18, 1928, she was an in-patient under Dr. A. M. H. Gray, at University College Hospital, for a persistent pustular dermatitis affecting the limbs, face, scalp, and to a less extent the trunk. A pure culture of *Staphylococcus aureus* was obtained from the lesions. She was treated by vaccines, iron, and arsenic, and a variety of liniments and proprietary foods containing vitamins.

On February 22, 1930, she became an in-patient under the Medical Unit at University College Hospital, when a diagnosis of pancreatic insufficiency was made. The total fat in the stools at that time was 71.2 per cent., of which 45.2 per cent. was neutral fat, and 26.0 per cent. fatty acid. The test meal showed free hydrochloric acid. The red blood-cells were 4,000,000 per c.mm.; haemoglobin, 68 per cent.; colour index, 0.85; white blood-cells, 4,200 per c.mm.

On June 9, 1930, she was admitted to the London Hospital complaining of diarrhoea and cramps in the hands and feet. For eight months she had passed six motions by day and six by night. The condition was painless, and was accentuated after food. The appetite remained excellent. The attacks of tetany began with tingling and cramp-like pains in the hands. The fingers then became stiff, and though the thumb was extended and adducted the fingers were flexed. For five months she had had amenorrhoea.

Clinical examination. Weight 7 st. 2 lb.; height 5 ft. 2 in. A pale, thin woman, with a dry skin and seborrhoea of the right eyebrow. There was no clubbing of fingers and no bone deformity. The Chvostek and Trousseau signs were positive. *Eyes:* slit-lamp examination showed fine scattered opacities throughout the lens; a few in the foetal nucleus (Mr. C. B. Goulden). She was deaf, and examination of the ears showed bilateral adhesive catarrh of both Eustachian tubes with fibrous ankylosis of the left ossicles, and two perforations of the left tympanum. The heart and lungs were normal. Blood-pressure, 110/70. There was slight distension of the abdomen. The liver was palpable 3 cm. below the costal margin on inspiration.

Special examinations. *Urine:* normal; no Bence Jones protein present. *Stools:* pale and porridgy in consistency; total fat, 71.2 per cent.; unsoaped fat, 67.0 per cent.; neutral fat, 45.2 per cent.; free fatty acid, 26.0 per cent.; combined fatty acid, 4.2 per cent. Serum calcium, 8.4 mg. per 100 c.c. Plasma phosphorus, 3 mg. per 100 c.c. Plasma phosphatase, 0.283 mg. *Test meal:* free hydrochloric acid, 0.27 per cent.; total acidity, 80. *Blood count:* red blood-cells, 4,000,000 per c.mm.; haemoglobin, 62 per cent.; colour index, 0.76; white blood-cells, 4,800 per c.mm.; polymorphs, 67 per cent.; lymphocytes, 24.5 per cent.; eosinophils, 4 per cent.; large mononuclears, 4.5 per cent. *Wassermann reaction:* negative.

Progress. She improved on a low-fat, high-vitamin diet, together with calcium lactate 10 grm. daily.

On January 21, 1931, she was readmitted to the London Hospital, complaining of diarrhoea, weakness, dyspnoea, palpitation, and scattered skin lesions.

Clinical examination. Weight 7 st. 6 lb. Chvostek sign positive. Trousseau sign negative. Slight icteric tinge of conjunctivae. *Tongue:* smooth, papillae pale and atrophic. Soft, light-brown hair, with a tendency to silver-grey. *Skin:* dry; large, moist, red abraded areas from 2 cm. to 8 cm. diameter on all limbs (Plate 36, Fig. 4), and to a lesser extent on trunk. Many of these lesions showed scaly brown pigmented borders. One lesion on the left calf showed a deep brown scaly periphery and a moist, red, abraded centre.

Special examinations. *Stools:* total fat, 39.8 per cent.; unsoaped fat, 15.6 per cent. No amoebae or cysts seen in the stools. Agglutination reactions negative for typhoid and dysentery organisms. Blood urea, 20 mg. per 100 c.c. *Sugar-tolerance test:* fasting blood-sugar, 0.064 per cent.; blood-sugar after 50 grm. of glucose by mouth—in 45 minutes 0.077 per cent., in two hours 0.08 per cent., no glycosuria throughout. *Test meal:* free hydrochloric acid, 0.22 per cent.; total acidity, 80. Serum calcium, 8.4 mg. per 100 c.c. Plasma phosphorus, 2.1 mg. per 100 c.c. Plasma phosphatase, 0.189 to 0.625 mg. *Calcium balance:* the calcium output was estimated in the urine and faeces for three three-day periods (Fig. 22). The patient was kept on a weighed diet of known low-calcium content (0.31 grm.). The calcium output in the urine was 0.04 grm.; that in the faeces was 0.91 grm. Controlled radiograms revealed no abnormality in the bones examined. Examination by

opaque enema showed a condition of megacolon in which four pints of barium sulphate were used, the whole colon being of poor tone and showing great enlargement of the lumen. *Blood count*: red blood-cells, 1,400,000 per c.mm.; haemoglobin, 62 per cent.; colour index, 1; white blood-cells, 3,200 per c.mm.; polymorphs, 63 per cent.; lymphocytes, 27 per cent.; eosinophils, 3 per cent.; large mononuclears, 7 per cent.; severe anisocytosis, punctate basophilia, poikilocytosis. Indirect van den Bergh reaction, 0.1 mg. per 100 c.c.

Progress. There was a rapid response to liver extract therapy, the reticulocytes reaching a level of 18.5 per cent., and the total red cell count 4,300,000 per c.mm. Nevertheless, the amenorrhoea persisted. The patient did not take the liver extract regularly, and the anaemia relapsed. She was therefore readmitted for intensive treatment of the anaemia on December 18, 1931. *Blood count*: red blood-cells, 3,300,000 per c.mm.; haemoglobin, 68 per cent.; colour index, 1.03; white blood-cells, 2,400 per c.mm.; polymorphs, 56 per cent.; lymphocytes, 39.5 per cent.; eosinophils, 3 per cent.; large mononuclears, 1.5 per cent.; platelets scanty; anisocytosis; no poikilocytosis; mean diameter of red cells, 7.782μ , just larger than the largest calculated normal mean of 7.718μ . The variability was 9.5 per cent., and there was 8.8 per cent. megalocytosis. The indirect van den Bergh reaction varied between 0.5 and 0.75 van den Bergh units. Urobilinogen not in excess in the urine.

She was given a high-calcium diet which contained meat and green vegetables and, in addition, 12 grm. of marmite daily. Irradiated ergosterol and calcium lactate were discontinued, to obtain as far as possible a pure marmite effect. Daily blood examinations were made. The reticulocytes started to rise on the sixth day, reaching a maximum of 10.8 per cent. on the ninth day, and then falling slowly to normal. The red blood-cells and haemoglobin rose steadily, the red blood-cells reaching a level of 4,000,000 per c.mm. 25 days after treatment was begun. They are now 5,000,000 per c.mm., and the haemoglobin is constantly in the neighbourhood of 80 per cent., while the indirect van den Bergh reaction is 0.25 van den Bergh units. The diarrhoea and tetany, which previously had been controlled, became extremely severe after irradiated ergosterol and calcium lactate were omitted, but in spite of this there was a gain in weight, and the improvement in the blood picture was rapid. Simultaneously with the improvement in the blood picture the skin lesions began to improve; the moist, red, excoriated areas dried up, leaving scaly brown pigmented lesions. On January 10, 1932, menstruation occurred for the first time in twenty-three months, but has since been extremely irregular. In spite of the good effects of treatment by marmite upon the anaemia, skin lesions, and amenorrhoea, diarrhoea and tetany recurred in February 1932, accompanied by pain in the lower ribs, right iliac bone, and right hip. Radiograms of these bones showed no osteoporosis nor fracture.

Case 9. (Hunter, 1930.) Idiopathic steatorrhoea, osteomalacia, tetany, dwarfism, hypochromic anaemia.

E. S., a single woman of 34 years. (L. H. Reg. No. 40440, 1928.) Referred to authors by Dr. M. M. Woods, of Balham.

Clinical history. She was born in Manchester at full term and was the first of four children. She was breast-fed for twelve months, and afterwards took badly to milk. At five months she cut her first tooth, and

at ten months she talked. At thirteen months she began to walk, when it was noticed for the first time that her knees were wrong. She was a small child. The first and second dentitions were apparently normal. At five years she began to go to school, but could never run because of her knees. She had occasional short attacks of diarrhoea.

As a child she was usually top of her class in school. As she approached the age of 14 she became weak and stopped growing, and she had vague symptoms of what she afterwards learned was tetany. One morning in March in the year she was 14, she awoke with her hands stiff and with pains in wrists, ankles, and knees. Characteristic carpo-pedal spasm occurred. Her hair began to get thinner and became greyish. There was no change in the skin or nails. Nine months later menstruation began. Subsequent periods have been normal in amount and somewhat irregular, with intervals of five or six weeks.

Between the ages of 16 and 24 she was semi-invalid and had to be wheeled about in a Bath chair. She then improved for a time, taking an interest in people and in books, but having to rest for a period every day. Attacks of tetany occurred about four or five times every winter and, later, sometimes in the summer. They had no relation to menstruation. Early attacks were confined to the hands and feet; later ones affected also the shoulders, knees, neck, and face. Sometimes she was unable to speak for short intervals, breathing was difficult, and the eyelids twitched. Pains and spasms lasted up to two or three hours. Subsequently the muscles felt stiff and aching and remained so for three or four days.

At the age of 28, she began to have attacks of epigastric discomfort with abdominal distension, flatulence, and diarrhoea. There was complete loss of appetite (she had never been able to take milk or bacon fat). The diarrhoea often lasted several weeks. Sometimes attacks of tetany were associated with these disturbances, though there was no constant time relation between the two.

There is no history of bone disease nor of dwarfism in the family.

Clinical examination (March 10, 1928). Height 4 ft. 3 in.; weight 5 st. 2 lb. She is a tiny woman, thin, with the general contours of an adult, except that her head is rather large in proportion. She is mentally normal, and unusually intelligent, but she has the shyness and sensitiveness of a dwarf. Her brow is wrinkled, and her expression anxious and a little pathetic. Voice, high and piping. *Skin*: pale, fine, and smooth; face freckled; no skin eruption. *Hair*: thin and very fine on the head, brown, and in places grey; normal on the pubes; very scanty in the axillae. *Tongue* normal. *Teeth*: double dentures; a few remaining molars. *Eyes*: slit-lamp examination of lenses showed collections of opacities similar to those seen in a case of post-operative tetany (Plate 41, Fig. 15). There are central flaky opacities with some small crystalline opacities, some chromatic. Powdery opacities are seen in the nucleus of the lens. (Mr. C. B. Goulden.) *Thyroid gland*: present and normal in size. *Hands*: small and delicate in proportion to the rest of the body, resembling those of a child of 14: no clubbing of fingers. *Trousseau sign* positive. *Chvostek sign* negative. *Knees*: marked genu valgum, more pronounced on the right side, and so severe that she can stand only with her legs crossed, the right in front of the left. When the knees are placed together side by side, the feet are separated by eight inches. *Spine*: straight. *Breasts*: normally developed. *Heart and lungs* normal. *Pulse* regular, 82. *Radial arteries* normal. *Blood-pressure* 145/90. *Abdomen*: rather protuberant, especially above the umbilicus.

Special examinations. *Urine:* normal; no Bence Jones protein present; diastase index, 5 units. Renal efficiency tests: blood urea, 0.028 per cent. Phenolsulphonephthalein excretion, 25 per cent., 12.5 per cent., 10 per cent., in successive hours. Urea concentration up to 3.36 per cent. *Sugar-tolerance test:* fasting blood-sugar, 0.080 per cent., blood-sugar after 50 grm. of glucose by mouth—at intervals of thirty minutes—0.080 per cent., 0.060 per cent., 0.074 per cent., 0.080 per cent., 0.080 per cent., 0.062 per cent. No glycosuria throughout. *Blood:* red blood-cells, 4,600,000 per c.mm.; haemoglobin, 62 per cent.; colour index, 0.67; white blood-cells, 6,320 per c.mm.; polymorphonuclear neutrophils, 58 per cent.; eosinophils, 0.5 per cent.; small lymphocytes, 26.5 per cent., large lymphocytes, 3.5 per cent.; large hyaline cells, 11.5 per cent. *Wassermann reaction:* negative. Serum calcium, 8.2 mg. per 100 c.cm. Plasma phosphorus, 2.4 mg. per 100 c.cm. Plasma phosphatase, 0.540 mg. *Fractional test meal:* achlorhydria. *Stools:* pale and porridgy; total fat, 60 per cent.; unsoaped fat, 40 per cent.; neutral fat, 19.3 per cent.; free fatty acid, 20.7 per cent.; combined fatty acid, 20 per cent. *Radiograms of bones:* there was a uniform diminution of density of all bones examined. The shafts of the tibiae were bent. The epiphyses were united. The metaphyses of many of the long bones showed faint transverse lines of increased density up to five in number. The pelvis was grossly deformed and beak shaped (Plate 38, Fig. 10). The calvaria was normal. *Calcium balance:* the calcium output was estimated in the urine and faeces for three three-day periods (Fig. 22). The patient was kept on a weighed diet of known low-calcium content (0.41 grm.). The calcium output in the urine was 0.29 grm.; that in the faeces was 0.83 grm.

Progress. The use of irradiated ergosterol (24,000 international units daily) raised the serum calcium to 12.1 mg. per 100 c.cm. The rise was greater with a high-calcium diet than with a low-calcium diet. When vitamin D was withdrawn the serum calcium dropped to 6.5 mg. per 100 c.cm. The decline was accentuated on a high-fat, low-calcium diet, when it reached 5.7 mg. per 100 c.cm. Tetany, of course, reappeared, but the use of ultra-violet irradiation rapidly raised the serum calcium level to 8.5 mg. per 100 c.cm. and abolished the tetany. During the four years of observation and treatment attacks of abdominal discomfort with diarrhoea and tetany have recurred every five or six months. During attacks of diarrhoea she has passed up to six stools a day. The effect of marmite on the anaemia was negative. Large doses of iron (90 grains of Bland's pill daily) have raised the haemoglobin from 58 per cent. to 88 per cent., the red cells being constantly in the neighbourhood of 5,000,000 per c.mm.

Case 10. Idiopathic steatorrhea, infantilism, latent tetany.

M. B., a single woman of 19 years. (L. H. Reg. No. 41987, 1931.) Referred to authors by Dr. George Riddoch.

Clinical history. Born in London. She was apparently normal until eight years of age, when she had measles, followed by a discharging right ear which left her rather deaf. At ten years it was noticed that she was not growing properly; the hands especially were remaining small. The bowels began to get very loose: at normal times she passes three motions a day, but in attacks passes up to five. The stools are always pale and loose, but not greasy. At ten years of age the hair of her scalp began to fall out, and has always been fine and short since. She has never menstruated. She got on well at school, and now works at inspecting parts in an

aeroplane factory. She takes a varied diet, and has had no trouble with her teeth. There is no history of bone disease in the family, neither has she ever broken a bone.

Clinical examination (January 26, 1932). Weight 5 st. 2 lb. Height 4 ft. 6½ in. She is a fairly well-proportioned but slightly dwarfed girl, with a fresh complexion. There is no wasting. The hair of the eyebrows and scalp is scanty (Plate 36, Fig. 3), and she wears a wig. The pubic and axillary hair is also scanty. There is normal development of the breasts. The teeth are good, and the tongue is normal. The mucous membranes are of normal colour. *Eyes*: no abnormality found on examination of lenses by slit-lamp. There is no clubbing of the fingers. The finger-nails are short and wide, and the terminal phalanges of the fingers too short. There is no skin eruption. Heart and lungs clear. Blood-pressure 116/80. *Abdomen*: normal. Chvostek sign positive. Trousseau sign negative. Bilateral deafness, especially in left ear. There is no bone deformity.

Special examinations. *Urine*: normal; no Bence Jones protein present; diastase index, 10 units. Blood urea, 0.022 per cent. *Stools*: pale; total fat, 55.5 per cent.; unsoaped fat, 38.4 per cent.; neutral fat, 10 per cent.; free fatty acid, 28.4 per cent.; combined fatty acid, 17.1 per cent. *Fractional test meal*: free HCl absent. Serum calcium, 10.1 mg. per 100 c.cm. Plasma phosphorus, 2.3 mg. per 100 c.cm. Plasma phosphatase, 0.166 mg. *Calcium balance*: the calcium output was estimated in the urine and faeces for two three-day periods (Fig. 22). The patient was kept on a weighed diet of known low-calcium content, 0.3 grm. The calcium output in the urine was 0.02 grm.; that in the faeces was 0.42 grm. *Radiograms of bones*: deformity of bones of hands; deficiency in length of shafts of metacarpals, increasing from first to fifth; non-development of second and fifth terminal phalanges; imperfect union of many epiphyses of bones of digits. Controlled radiograms revealed no abnormality in the density of calcification. *Blood count*: red blood-cells, 4,900,000 per c.mm.; haemoglobin, 80 per cent.; colour index, 0.81; white blood-cells, 4,600 per c.mm.; polymorphs, 57 per cent.; lymphocytes, 39 per cent.; eosinophils, 1 per cent.; large mononuclears, 2 per cent. *Wassermann reaction*: negative. *Sugar-tolerance test*: fasting blood-sugar, 0.066 per cent.; blood-sugar after 50 grm. of glucose by mouth—at intervals of thirty minutes—0.074 per cent., 0.069 per cent., 0.063 per cent., 0.066 per cent., 0.058 per cent., 0.044 per cent. No glycosuria throughout.

Case 11. Idiopathic steatorrhoea (since childhood), tetany.

G. C., a man of 35 years. (L.H. Reg. No. 31803, 1930.) Referred to authors by Dr. James Collier, from the National Hospital, Queen Square.

Clinical history. Born in London. Never had rickets or tetany in childhood. His mother said he had 'consumptive bowels' as a child. She told him that he had to wear napkins until he was 7 years old because of diarrhoea. He left school at 14, and served four years in Flanders in the war of 1914-18, remaining perfectly well. Eight years ago he noticed that his motions were never properly formed, and were never dark enough. Six years ago he began to get attacks of diarrhoea. This was painless; the stools were of a pale colour like porridge. He had three stools before breakfast, and six more during the rest of the day. In February 1929, he began to get tinglings like pins and needles in the legs. In April 1929, he began to get twitching of the face, especially under the eyes, with a numb feeling which passed to the top of the head. He also had tingling sensations in the

arms and hands. The hands would go stiff, with the thumb tucked into the palm, and the fingers straight. The wrists and elbows would be bent, and the tips of the fingers approach the armpit. Attacks would last up to twenty-four hours, and he might get them daily or be free for four days at a time. Since 1919 he has been a rubber-hose worker, but in December 1929 he gave up work because when he gripped the roller he could not let go except by pulling the thumb away with the other hand. In addition the attacks gave rise to a lot of pain in the wrists, with puffiness of the skin.

In August 1930 he was admitted to the National Hospital, Queen Square, under the care of Dr. James Collier. While there he had four attacks of tetany, and he was treated by artificial sunlight and calcium injections. He had lost sixteen pounds in weight in two years.

Clinical examination (November 26, 1930). Spare, somewhat wasted, muscular man. Weight 8 st. 4 lb. Height 5 ft. 2 in. Slight genu varum with separation of inner aspects of knees by $1\frac{1}{2}$ in. Slight bowing of tibiae with convexity outwards, and also forwards. Other bones straight. Slight clubbing of fingers. No jaundice. No pallor of skin or mucous membranes. *Tongue*: normal. Slight caries of teeth. Abraded erythematous area 4 in. in circumference over left great trochanter. *Eyes*: no abnormality found on examination of lenses by slit-lamp. Chvostek sign and Trousseau signs positive. Pulse regular, 82. Arteries normal. Blood pressure 125/80. Heart and lungs normal. Uniform slight distension of abdomen.

Special examinations. *Urine*: normal; no Bence Jones protein present; diastase index, 10 units. *Stools*: pale and porridgy; total fat, 48.7 per cent.; unsoaped fat, 24.2 per cent.; neutral fat, 11.1 per cent.; free fatty acid, 13.1 per cent.; combined fatty acid, 24.5 per cent. *Test meal*: free HCl 0.15 per cent., total acidity 52. Serum calcium 5.1 mg. per 100 c.c. Plasma phosphorus 2.3 mg. per 100 c.c. Plasma phosphatase 0.356 mg. *Radiograms of bones*: controlled radiograms revealed no abnormality in bones examined. *Blood count*: red blood-cells, 5,000,000 per c.mm.; haemoglobin, 80 per cent.; colour index, 0.80; white blood-cells, 3,400 per c.mm.; polymorphs, 71 per cent.; lymphocytes, 22 per cent.; eosinophils, 4 per cent.; large mononuclears, 3 per cent. *Wassermann reaction*: negative. Blood urea, 0.021 per cent. *Sugar-tolerance test*: fasting blood-sugar 0.067 per cent.; blood-sugar after 50 gm. of glucose by mouth—in forty-five minutes—0.077 per cent., in two hours 0.069 per cent. No glycosuria throughout.

Progress. Large doses of parathormone, up to sixty units daily for several weeks, had no effect on the tetany nor on the level of the blood calcium. Later he was kept completely free from tetany by means of ultra-violet irradiation, the continued use of which raised the serum calcium to 9 mg. per 100 c.c., and the plasma phosphorus to 3.3 mg. per 100 c.c. He was kept on a low-calcium diet, together with 10 gm. of calcium lactate a day. In spite of this, relapses of diarrhoea occurred every four months or so. The diarrhoea was controlled by means of bismuth oxycarbonate, and he remained well enough to continue at work, no longer disabled by tetany.

Case 12. Idiopathic steatorrhoea, tetany, osteomalacia.

B. C., a married woman of 57 years. (L.H. Reg. No. 40058, 1931.) Referred to authors by Dr. W. A. Lister, of Plymouth.

Clinical history. Born in Plymouth. She was well until June 1927, when she had three attacks of colic in the right hypochondrium with sweating. Loss of weight; she thinks she weighed only five stone. Constipation, no

pale stools. August 1927: laparotomy by Mr. G. Robinson (Plymouth); cholecystotomy—drainage of gall bladder, no calculi found. Three weeks after this operation bilateral femoral thrombosis occurred, and severe diarrhoea began. She passed up to sixteen pale watery motions a day. The diarrhoea lasted one year, and left her so weak that she had to be carried about. Treatment by kaolin did not improve it. January 1930: about the time the diarrhoea was getting better under treatment, she began to get cramps in the legs, which were so severe that she could not get her legs out straight. The fingers became numbed and were clasped one against the other. At this time she became unable to walk. Other attacks of tetany occurred during the same winter, and lasted up to twenty minutes. Immediately following the tetany she began to have pain in the bones of the pelvis and in the ribs, especially on the right side. Pain sometimes occurred in other bones, especially on turning in bed or on pressure. She became unable to carry a tray or to hold a handbag. Dr. W. A. Lister found an excess of fat in the stools and ordered radiograms, which showed well-marked distortion and asymmetry of the pelvis. She was treated by means of a low-fat diet, together with calcium lactate and tablets of irradiated ergosterol. After three months of such treatment the pains in the bones persisted, and she was sent to London. Catamenia commenced at 15, and ceased at 53. Has one son aged 19, and had no other pregnancy. There is no history of bone disease in the family.

Clinical examination (January 9, 1931). Weight 7 st. 11 lb. Height 5 ft. 1½ in. Walks with difficulty, bent forward and limping. Ill nourished, but not pale. No skin eruption, no abnormality of hair, no clubbing of fingers, finger-nails brittle. Double dentures; six remaining teeth normal. Senile changes in lenses, with water clefts. Chvostek and Trousseau signs negative. Chest is squat, the space between the subcostal margin and the iliac crest being diminished. Slight scoliosis with thoracic convexity to right. Long bones not deformed. Bones are tender on pressure, especially over right lower ribs and right scapula, forearms, and pelvis. There is no tenderness on pressure over the spine, left scapula, humeri, and hands. Heart and lungs normal. Blood-pressure 160/90. *Abdomen*: right upper paramedian scar; no tenderness, no distension.

Special examinations. *Urine*: normal; no Bence Jones protein present; diastase index, 20 units. *Stools*: pale and porridgy; total fat, 67·5 per cent.; unsoaped fat, 18·0 per cent.; neutral fat, 2·1 per cent.; free fatty acid, 15·9 per cent.; combined fatty acid, 49·5 per cent. *Test meal*: free HCl 0·08 per cent., total acidity 27. Serum calcium 8·6 mg. per 100 c.c. Plasma phosphorus 1·8 mg. per 100 c.c. Plasma phosphatase 0·718 mg. *Calcium balance*: the calcium output was estimated in the urine and faeces for three three-day periods (Fig. 22), the patient being kept on a weighed diet of known low-calcium content (0·31 grm.). The calcium output in the urine was 0·05 grm.; that in the faeces was 0·71 grm. *Radiograms of bones*: controlled radiograms of bones showed considerable diminution of calcification in all bones examined. Cortices of radius, ulna, metacarpals, tibia, and fibula were thinner than in the control, and showed in places trabeculation. The left side of the pelvis showed gross deformity, with flattening opposite the acetabulum, and a fracture through the superior ramus of the os pubis on each side. There were also fractures, without displacement, of the left tenth rib and of the left ulna. Radiograms of the kidneys and urinary tract were normal. *Blood count*: red blood-cells, 5,400,000 per c.mm.; haemoglobin,

70 per cent.; colour index, 0.63; white blood-cells, 8,200 per c.mm.; polymorphs, 66.5 per cent.; lymphocytes, 29 per cent.; large mononuclears, 4 per cent.; basophils, 0.5 per cent.; reticulocytes, 0.8 per cent.; anisocytosis, poikilocytosis, polychromasia slight but definite. *Wassermann reaction*: negative. *Sugar-tolerance test*: fasting blood-sugar 0.078 per cent., blood-sugar after 50 grm. of glucose by mouth—at intervals of thirty minutes—0.071 per cent., 0.069 per cent., 0.100 per cent., 0.100 per cent., 0.100 per cent., 0.090 per cent., 0.095 per cent. No glycosuria throughout.

February 5, 1931: operation (Mr. R. Milne): a piece of bone was removed from the inner aspect of the right tibia. Periosteum, corticalis, and a portion of spongiosa were included.

Pathological Report. (Professor H. M. Turnbull.) Tissue removed at operation (S.D. 329, 1931)

Macroscopic examination. A longitudinal slice of bone, 5.5 cm. long. Most of the outer surface was covered with periosteum. Beneath this the cut surface showed 0.2 cm. of white compact bone and 0.4 cm. of lace-like, small-meshed spongiosa containing red marrow.

Microscopic examination. The specimen was divided transversely after fixation in 4 per cent. saline formaldehyde, and the two pieces were placed in Müller's solution. After two months one piece was further decalcified for 2½ hours in 5 per cent. nitric acid, and was embedded in celloidin.

The cortex is traversed by numerous longitudinal Haversian spaces. In its outer part these are frequently as wide or wider than the trabeculae that bound them; in its inner part they are much wider and anastomose more extensively. The cortex consists, therefore, of a spongy instead of the normal compact bone. Many of the outer Haversian spaces are open towards the periosteum in part of their course, so that the outer layer of cortex is frequently interrupted for considerable distances. The inner part of the cortex merges into a spongiosa composed of a few widely separated slender trabeculae, which are in general directed longitudinally. A finely fibrillated, fibrous marrow in the spaces close to the periosteum gives place deeper to an adipose marrow in which there is much recent extravasation of blood. There is no haematogenous marrow. Schmorl's thionin stain for fibrillae shows one small interstitial system of woven bone; the rest of the bone is lamellar. There is no excessive mosaic of lamellar systems. Except in a few small spots the trabeculae are covered and the Haversian canals are lined with a seam of osteoid tissue. Very few of these seams, where cut at right angles to their surface, are within the normal limits of depth; many are three or more times as deep as the deepest in actively growing infants. This excess of osteoid tissue above the normal is exaggerated in many places by oblique section, so that it is a very conspicuous feature in the general picture. A single layer of flat osteoblasts at a variable distance from one another lies upon the surface of the seams. Osteoclasts are present in considerable number. Most lie in lacunae, and these usually indent calcified bone. In two places a group lies within an eroded bay, and each bay contains a focal patch of fibrous marrow.

Remarks. The bone shows conspicuous osteoporosis combined with conspicuous osteomalacia. It is not possible to decide whether this porosis is the result of excessive resorption, deficient apposition, or a combination of both. It is only possible to say that, at present, in this portion of bone, active resorption by osteoclasts is undoubtedly greater than normal, but

that eroded areas are very few in comparison with the extensive stretches of deep osteoid seams or systems covered by osteoblasts, whilst apposition, as judged by the form and number of the osteoblasts, is not appreciably more active or less active than in the spongiosa of normal adults. There is now no evidence of unusually rapid apposition, so that, if apposition has previously been at the same rate, the arrest of calcification has been present for a considerable time. The recent haemorrhage doubtless occurred during the excision of the specimen. (H. M. T.).

Progress. She was given a low-fat, high-calcium diet, with the addition of calcium lactate (10 gm.) and 30,000 international units of irradiated ergosterol daily. When she left hospital, three weeks after commencement of treatment, she could only just climb the stairs and had to be lowered by a maid into the bath. After one week she did the whole of the cooking at home, and gradually took on full household duties. At the end of a month at home she could walk up forty stairs to her bedroom. Difficulty in walking downstairs persisted. Sometimes on walking she got a stiff feeling in the muscles of the thighs, and in the knees and ankles. Starting to walk after getting up from a chair remained painful. The diarrhoea has not been abolished, and may occur for two days at a time; she then passes up to sixteen stools a day and may lose six pounds in weight during an attack. She is often free six weeks between attacks. The abdomen gets swollen during attacks.

February 17, 1932. *Radiograms of bones.* The same bones as before were selected and the same control used. The degree of calcification seemed to be identical with that seen in previous radiograms. The fracture in the centre of the left ulna had united, and the old mottled fracture of the pubis had not only united but was also more definite in outline.

Stools: total fat, 54.9 per cent.; unsoaped fat, 34.6 per cent. Patient was advised to continue with high-calcium, low-fat diet, together with 30,000 international units of irradiated ergosterol daily, and in addition to arrange for treatment at home by ultra-violet irradiation. In spite of this she suffered a severe relapse.

February 20, 1932. Extract from letter: 'I am sorry to say I feel sadly ill, and am dreadfully stiff, I feel as if my rib on the left side is broken. I cannot turn in bed without the same old pain.'

March 8, 1932. 'I have been stiff and poorly, my side may be a little easier, but to get out of a chair and start to walk is almost as painful as last year. The insides of my thighs are so stiff. I simply can't make myself move properly.'

April 10, 1932. 'I am obliged to use a stick to crawl about the house. The pain in my left side is better, but the right side is very painful when I turn in bed or raise my arms. The very painful part is down the inside of my right thigh, especially when I get up to walk.'

Case 13. Coeliac infantilism, osteomalacia, tetany.

W. E., a boy of 19 years. (L. H. Reg. No. 30295, 1932.) Referred to authors by Dr. Macdonald Critchley, from the National Hospital, Queen Square.

Clinical history. Born in Surrey. He developed normally for eighteen months. He toddled and sat up and walked at the same times as the other children. At eighteen months he had 'consumptive bowels'. The abdomen was swollen, and the motions were putty-coloured but not excessive. Usually the bowels are regular and open once daily on the average. If he

eats fruit or fats he tends to get diarrhoea, when the stools become a pale grey-brown colour, but are neither greasy nor very bulky. When the diarrhoea passes off they are a little bit darker, but never normal in colour. He got on fairly well at school, and left at the age of 14 when in the fifth standard. He was always smaller than other boys. He has never shaved. No erection of the penis has occurred. Five years ago he first noticed scaly pigmented patches on the skin, the right arm below the shoulder being first affected. This patch got better after two years or so. Eighteen months' slight general weakness with pain in various parts of the body, most marked in the ankles. These pains first affected the feet, then the trunk, the knees and the arms last of all. They are dull and aching in character and are felt in the joints and muscles, but not in the bones. They are not constant, and they only come on when he is moving about. Apparently he gets stiff when at rest, and then when afterwards he walks about he feels pains in his joints which gradually wear away. Twelve months ago he began to have attacks of cramp in the hands and legs. Originally about three attacks occurred every week. The fingers become cramped together and the wrists bent, the effect wearing off in ten minutes. The toes do not get drawn up, but cramps occur in the calf muscles. On two occasions when the spasms were severe he experienced difficulty in breathing or speaking for a second or two. He has recently been apprehensive and easily frightened and occasionally has had a fit of weeping. No history of fractures. No history of bone disease or of dwarfism in the family.

Clinical examination (February 14, 1932). Height 4 ft. 7 in. Weight 4 st. 1 lb. He is strikingly infantile, so that, though aged 19, his height is that of a boy of 12. Not only is he small in stature, but his whole development is reduced in proportion, so that he appears as a youth in miniature. There is no hair on the face, the skin of which is rather sallow. Slight patches of brown pigmentation rather larger than freckles on face and abdomen. Skin everywhere dry and rather translucent. Patch of rough, striated, brown-pigmented skin, 2 by 3 cm., in front of left ankle. Hair of scalp is buff-greyish colour. No pubic or axillary hair. Very small penis and testicles, equivalent to age of 5. Voice high and piping. Smooth tongue with areas of papillary atrophy. Early clubbing of fingers. *Teeth*: excellent, two small amalgam fillings. *Eyes*: visual acuity normal. Slit-lamp examination of lenses: there are a few fine scattered opacities in the lens in the peripheral part of the adult nucleus (which is in process of formation); in the right lens in one place an opacity is seen near to the surface (Mr. C. B. Goulden). Trousseau sign positive. Chvostek sign positive. *Skull*: circumference 19½ in., marked central bossing in frontal region, also on vertex and occiput. Depression in front of vertical boss over site of anterior fontanelle. *Spine*: normal. Considerable rickety rosary, other epiphyses apparently not enlarged. Definite genu valgum. Ankles separated two inches when knees placed together. Heart and lungs normal. Pulse regular, 84. Radial arteries normal to palpation. Blood-pressure 105/80. *Abdomen*: marked distension, especially above umbilicus, causing outward bulging of lower ribs. Liver and spleen not felt.

Special examinations. *Urine*: normal; no Bence Jones protein present; diastase index two units. *Stools*: pale yellow-brown; total fat, 45.6 per cent.; unsoaped fat, 38.7 per cent.; neutral fat, 13.3 per cent.; free fatty acid, 25.4 per cent.; combined fatty acid, 6.9 per cent. Serum calcium, 5.9 mg. per 100 c.c. Plasma phosphorus, 5.8 mg. per 100 c.c. Plasma

phosphatase, 0.425 mg. *Calcium balance*: the calcium output was estimated in the urine and faeces for two three-day periods (Fig. 22), the patient being kept on a weighed diet of low-calcium content (0.31 grm.). The calcium output in the urine was 0.02 grm.; that in the faeces was 0.17 grm. *Radiograms of bones*: there is a striking diminution of density of all bones as examined by the controlled method (Plate 41, Fig. 14). The corticales of the long bones are thin and trabeculated. The spongiosa is wide-meshed. Brim of pelvis slightly deformed on left side. Transverse lines of increased density up to two in number in metaphyses of many long bones. Absence of pale cup-like areas in metaphyses, but great delay in union of epiphyses, especially in bones of hand (Plate 40, Fig. 13), head of femur, and acetabulum. Calvaria shows no increased thickness, but the whole shadow of the skull is poor and finely mottled. Healing transverse fractures in upper ends of right tibia, left tibia and fibula, and in lower end of right ulna. Radiograms of the kidneys and urinary tract are normal. *Blood count*: red blood-cells, 4,500,000 per c.mm., haemoglobin, 66 per cent.; colour index, 0.73; white blood-cells, 4,200 per c.mm.; polymorphs, 69 per cent.; lymphocytes, 23 per cent.; large mononuclears, 2.5 per cent.; eosinophils, 5.5 per cent.; reticulocytes, 0.4 per cent. *Wassermann reaction*: negative. *Sugar-tolerance test*: fasting blood-sugar, 0.079 per cent.; blood-sugar after 50 grm. of glucose by mouth—at intervals of thirty minutes—0.090 per cent., 0.093 per cent., 0.108 per cent., 0.099 per cent. No glycosuria throughout. Blood urea, 0.024 per cent.

Case 14. Coeliac rickets, infantilism, tetany, hypochromic anaemia.

W. H., a boy of 16 years. (L.H. Reg. No. 30387, 1932.) Referred to authors by Mr. A. C. Gairdner.

Clinical history. Born in London. He was normal until the age of 10 months, when he began to suffer from diarrhoea and wasting. Since that attack he has had many others in which his bowels are open up to six times daily, the motions being pale in colour. At 18 months he began to walk, but was rejected for school at 5 years of age because he could not yet walk properly. At 6 he had a particularly severe attack of diarrhoea with much wasting. At 9 he used to walk a little in the house and went to school with his brother, who usually carried him. He attended school until the age of twelve. At 10 he was sent to the London Hospital by the school doctor, who claimed that the liver and spleen were enlarged. He was then well nourished but anaemic. The subcostal margins were splayed out. No other bone deformities were recorded. The abdomen was distended, and the liver and spleen just palpable. Ascites was suspected, but paracentesis abdominis revealed no fluid. *Blood count*: red blood-cells, 3,300,000 per c.mm.; haemoglobin, 45 per cent.; colour index, 0.68; white blood-cells, 7,320 per c.mm. At 12 he was thought to be suffering from abdominal tuberculosis and attended a tuberculosis dispensary for 10 months. Marmite was added to his diet. He was ultimately discharged with a statement that he did not suffer from tuberculosis. At 14, following a cold in the head, he began to have cramps in the hands and feet. They come on in cold weather more particularly. The fingers and thumb are cramped together, with the wrist and elbow bent. The feet are turned inwards and the toes drawn up. The knock-knee is of long standing, but has recently progressed rapidly. The mother states that during his childhood she took him to almost every hospital in London for rickets. No history of bone disease or fractures in the family.

Clinical examination (16 March, 1932). Weight 3 st. 6 lb. Height 3 ft. 10 in. Can stand with support, but is unable to walk. Considerable deformity and anaemia. The patient is a timid, dwarfed figure the size of a boy of 8, unable to read or write (Plate 35, Fig. 2). Definite clubbing of toes, slight of fingers. Abundant fine hair on scalp; none on face, axillae, or pubes. Penis and testicles small as in a boy of 6. *Skin*: pale, smooth, and delicate, no eruption. *Teeth*: normal; certainly not hypocalcified. *Tongue*: pale but otherwise normal. *Eyes*: slit-lamp examination of lenses—some fine, bright opacities in the adult nucleus, so far as this is formed at present (Mr. C. B. Goulden). Chvostek sign positive. Trousseau sign negative. Receding brow. Prominent occiput. Bossing of parietal bones immediately above ears. Circumference of skull 20 in. *Spine*: slight scoliosis in upper thoracic region. Very prominent sacrum. Gross rickety rosary (Plate 37, Fig. 7), lower ribs splayed out with wide subcostal angle. Deformity with forward bowing of both clavicles. Bowing of forearms with marked thickening of epiphyses at wrists. Severe genu valgum and thickening of epiphyses at ankles. Five inches separation at ankles when knees together. Hypotonia of muscles at all joints. Very great distension of abdomen. Divarication of recti with small umbilical hernia. Tip of spleen palpable. Heart and lungs normal. Radial arteries normal to palpation. Blood-pressure 105/65. Pulse regular, 86.

Special examinations. *Urine*: normal; no Bence Jones protein present. Blood urea, 0.037 per cent. *Sugar-tolerance test*: fasting blood-sugar, 0.054 per cent.; blood-sugar after 50 grm. of glucose by mouth—at intervals of 30 minutes—0.105 per cent., 0.086 per cent., 0.064 per cent., 0.066 per cent., 0.060 per cent., 0.083 per cent. No glycosuria throughout. *Blood count*: red blood-cells 4,600,000 per c.mm., haemoglobin 36 per cent., colour index 0.39, white blood-cells 4,200 per c.mm., polymorphs 51 per cent., lymphocytes 45 per cent., large mononuclears 1 per cent., basophilic cells 1 per cent., eosinophils 2 per cent. The red cells are pale; anisocytosis is present, with an occasional megalocyte and many microcytes; poikilocytosis. *Wassermann reaction*: negative. *Stools*: pale yellow-brown; total fat 50.7 per cent.; unsoaped fat 31.2 per cent.; neutral fat 8.8 per cent.; free fatty acid 22.4 per cent.; combined fatty acid 19.5 per cent. Serum calcium 8.6 mg. per 100 c.c. Plasma phosphorus 2.3 mg. per 100 c.c. Plasma phosphatase 0.645 mg. *Radiograms of bones*: there is striking diminution of density of all bones examined. The eleventh and twelfth left ribs and twelfth right rib are fractured. The right clavicle shows an old fracture with angular deformity, and the shafts of the right fibula and right ulna are bowed. The pelvis is triradiate and grossly deformed, the region of the acetabulum having been pushed in. At the growing ends of the long bones, especially lower end of radius, tibia, and fibula, there are wide, splayed out, cup-like, pale spaces. There are transverse lines of increased density up to seven in number in the metaphyses of many long bones, most marked in the lower end of the right tibia. Calvaria shows no increased thickness. The carpal and metacarpal bones are infantile. Union of the bones round the acetabulum is grossly delayed. Radiograms of the kidneys and urinary tract are normal. Opaque enema examination: the lumen of the colon is normal, but the total length of the gut is long, chiefly because of increased length of the sigmoid. *Calcium balance*: the calcium output was estimated in the urine and faeces for three three-day periods (Fig. 22). The patient was kept on a weighed diet of known low-calcium content (0.32 grm.). The calcium output in the urine was 0.02 grm.; that in the faeces was 0.84 grm.

Progress. A high-calcium, low-fat diet was given, together with 3,000 international units of irradiated ergosterol daily. Simple splints were applied to the outer aspects of each lower limb, to correct the genu valgum; the patient was soon encouraged to walk alone. No further attacks of tetany occurred, and the serum calcium rose to 9.2 mg. per 100 c.c. In a short time he learned his letters and was able to read simple words and to tell the time. The anaemia was treated by large doses of marmite without effect. When given Bland's pill gr. 40 daily the haemoglobin rose from 34 per cent. to 80 per cent. in a month with accompanying clinical improvement.

Case 15. Idiopathic steatorrhoea, tetany, osteomalacia. Death.

W. P., a man of 56 years. (L. H. Reg. No. 31817, 1929.) Referred to authors by Lord Dawson of Penn.

Clinical history. He was born in Brixton and has always lived in London. As a boy he was quite healthy at school and played games. At 13 he began to be knock-kneed. The deformity apparently increased fairly quickly. Nevertheless, he went to work. At 16 he was admitted to Guy's Hospital for osteotomy of each femur. At 17 he fell, causing a fracture of the left femur at the site of the osteotomy. He was readmitted to Guy's Hospital, where a splint with extension was applied. After three weeks he was discharged with the limb in good position. From 17 to 21 he was in indifferent health, and complained of weakness and lassitude. His doctor said he suffered from anaemia. No special treatment was prescribed. He was at work as a clerk all the time. From 21 to 49 he was healthy, fond of walking and cycling, and used to walk up to ten miles in an afternoon. In June 1922, at the age of 49, he began to complain of abdominal pain with flatulence and distension of the abdomen, and occasional vomiting. There was no haematemesis. The bowels were open about twice a day, the stools being sometimes yellow-brown and sometimes putty-coloured. In October 1922 he was admitted to Guy's Hospital, having lost 28 lb. in weight in three months. The abdomen was distended. Opaque meal examination was negative. The fractional test meal showed complete achlorhydria. He was provided with an abdominal belt and improved after six months. From 49 to 54 he was well except for occasional attacks of flatulence lasting a day or two. In November 1927, at the age of 54, he began to suffer from weakness, and to pass normal coloured, loose motions, up to three or four times a day. The illness was taken to be 'enteritis'. It persisted with varying severity for seven months. By the following summer he was well again. In March 1928, during periods of diarrhoea, he began to have attacks of stiffness of the fingers, twitching of the face, and slight difficulty in speech and swallowing. At first there was some alarm, because he was thought to have had a paralytic seizure. One attack lasted about four hours. The muscles were stiff rather than painful. Sometimes, and more especially at the end of the winter, he was unable to write for several weeks. October 1929: attacks of stiffness in hands and arms, accompanied by stiffness of legs. Bowels open twice a day, stools usually yellow-brown, but at times putty-coloured and frothy. Weakness has been increasing, and on admission to hospital he was finding it very tiring to walk. Appetite good. Some loss of weight. There was no history of bone disease in the family.

Clinical examination (November 25, 1929). Weight 6 st. 10 lb. Height 5 ft. 1 in. A thin, poorly-nourished man, with sallow complexion and deeply sunken eyes. Hair abundant and normal in distribution. Slight clubbing of

fingers and toes. No skin eruption. Mucous membranes, normal colour. *Tongue*: clean and moist. *Eyes*: no abnormality found on examination of lenses by slit-lamp. *Ears*: both tympanic membranes intact but retracted. Slight deafness in both ears. Condition resembles so-called chronic middle-ear catarrh, not otosclerosis (Mr. Norman Patterson). Several carious teeth. Chvostek sign negative. Trousseau sign positive. Pulse regular, 80. Arteries normal. Blood-pressure 120/90. Heart and lungs normal. Wide subcostal angle. Distension of abdomen. Great outward and slight anterior bowing of femora, especially in lower third. External rotation of anterior surface of tibiae, the left being slightly bowed forward. Osteotomy scars (2 cm. long) on inner aspect of each thigh in lower third. Bilateral hydrocele.

Special examinations. *Urine*: normal; no Bence Jones protein present. *Stools*: formed, clay-coloured; total fat, 52 per cent.; unsoaped fat, 27 per cent. *Fractional test meal*: trace of free HCl. Serum calcium, 6.3 mg. per 100 c.c. Plasma phosphorus, 2.3 mg. per 100 c.c. Plasma phosphatase, 0.241 mg. *Blood count*: red blood-cells 5,000,000 per c.mm.; haemoglobin, 85 per cent.; colour index, 0.85; white blood-cells, 11,120 per c.mm.; polymorphs, 65 per cent.; lymphocytes, 29 per cent.; eosinophils, 1 per cent.; large mononuclears, 5 per cent. *Wassermann reaction*: negative. Blood urea, 0.032 per cent. Fasting blood-sugar, 0.080 per cent. *Radiograms of bones*: controlled radiograms revealed slight loss of density in all bones examined, the metaphysis in many cases being more affected than the diaphysis. Great deformity with bowing of necks and shafts of femora.

Progress. He was given a diet containing about 1 grm. of calcium per day, together with 3,000 international units of irradiated ergosterol daily. The serum calcium and plasma phosphorus figures, however, remained low, and though attacks of tetany occurred only once or twice the Trousseau sign remained positive. He became weaker, and four weeks after admission to hospital developed mental confusion with dirty habits. This was not controlled by intramuscular injections of calcium gluconate. He became drowsy and had two attacks of difficulty in breathing, possibly due to laryngeal tetany, in the second of which he died.

Professor H. M. Turnbull has kindly given us the following abstracts from an account of the findings at necropsy which it is proposed to publish elsewhere.

Summary of Necropsy. (P.M. 464, 1929)

Broncho-pneumonia. Severe parenchymatous degeneration of kidneys. Sub-acute ulcerative enteritis. Intracellular anisotropic fat in liver and kidneys. Active gastric and pancreatic digestion and absorption of fat. Osteomalacia with deformities, and osteoporosis of skeleton. Normal erythropoiesis in marrow. Healed infarctions of cortex of right suprarenal body. Atrophy of spleen and liver. Epithelial proliferation and desquamation in atrophied thyroid gland. Slight atrophy of brain. Normal parathyroid bodies. Thymus masked by adipose tissue. Chronic appendicitis with adhesions. Slight atheroma of aorta; considerable degeneration of arteries within organs. Myoadenoma (1 cm. diameter) in right lobe of prostate. Bilateral hydrocele; cyst in head of right epididymis. Scars of operations for osteotomy of femora. Slight clubbing of fingers and toes. Greatly wasted man (39.56 kilo.; 1.55 metre) with deeply sunken eyes.

Skeleton

Macroscopic examination. There was slight lateral constriction of the thorax at the level of the fifth and sixth ribs. The femora were conspicuously bowed forwards and outwards at the start of their lower thirds, and their heads were depressed downwards, the upper border of the head being only 0.5 cm. above the upper border of the great trochanter. The anterior surfaces of the tibiae looked more directly forwards than normally, and the left bone was bowed considerably forwards just below its centre.

Microscopic examination. Thin bony plates and slender trabeculae were removed with forceps from the spongiosa of the upper and lower ends of a half of the left femur that had been placed in formaldehyde, but had not been decalcified. When examined microscopically without staining, almost all showed in places excessively deep osteoid seams upon their outer surfaces or lining Haversian spaces. Most fragments were then stained in silver nitrate to confirm the estimated distribution of calcification. The costal end of the right fourth rib, the neck and centre of the shaft of the right femur, the body of the fourth lumbar vertebra, and part of the sternum and of a parietal bone were fixed in formaldehyde and decalcified in Müller's fluid, followed in some instances by a 1 in 200 solution of nitric acid in Müller's fluid. All bones show a definite excess of osteoid tissue. The excess is most widely distributed in the spongiosa. It appears to be greatest in the spongiosa of the vertebra, and of a small centre of ossification in the costal cartilage. In the vertebra, the relatively great excess is explained by the frequency of tangential section of the seams. In the compacta of the femur and of the parietal bone the osteoid tissue is more focal and is confined to many Haversian spaces and occasional Haversian canals. When it is found in Haversian canals it usually forms the whole Haversian system. Excessively deep osteoid seams also lie here and there upon the inner surface of the corticalis.

Immediately round the small secondary centre of ossification in the costal cartilage, and about vessels that extend for a short distance from it, the cartilaginous matrix has lost its affinity for haematoxylin, whilst the cells show varying degrees of shrinkage and necrosis to complete disappearance. There is no provisional proliferation of cartilage cells and no chondral calcification. In a process of endochondral ossification of this kind the abnormalities caused by rickets in the growing ends of long bones cannot be expected.

In addition to the excess of osteoid tissue there is much osteoporosis. Thus, the corticalis of the rib and of the neck and centre of the femur is porous owing to many longitudinal Haversian spaces. The corticalis of the rib, vertebra, and sternum is abnormally thin. The trabeculae of the spongiosa in all these bones are abnormally slender and sparse. In the parietal bone there is much less evidence of porosis. The tables are thick and are more compact than the corticalis elsewhere, whilst the trabeculae in the diploë are stouter and form a closer net than in the spongiosa of the other bones. There is, however, one group of large irregular spaces eroded in the outer table.

Schmorl's thionin method for canaliculi and fibrils shows that woven, coarse-fibred bone is present only in situations and amounts similar to those in normal adult bones. The osteoid seams are covered by a layer of flat osteoblasts. Only one or two osteoclasts could be found.

Remarks. The skeleton shows very definite evidence of osteomalacia combined with osteoporosis. The occurrence of rickets in infants and in young children suffering from coeliac disease is well recognized (Parsons, 1932). The histological identity of rickets and osteomalacia was shown by Pommer (1885) in his classical work and was confirmed by Schmorl (1905). It has not yet been proved that the rickets which usually affects children is identical in cause with the osteomalacia which usually affects adults. It is probable that both conditions are due to a deficiency of vitamin D, but it is possible that most cases of osteomalacia in adults, and a few cases of rickets in children, differ from ordinary rickets in children, in that a deficiency of calcium is an additional factor (Turnbull, 1932). In any case there can be little doubt that the osteomalacia in this adult with coeliac disease is identical in cause with the rickets that affects children suffering from coeliac disease, the term osteomalacia merely signifying that, owing to the cessation of endochondral ossification, the epiphyseal changes characteristic of rickets are absent. Skeletal deformities had been observed in this patient since he was 13 years of age. He was suffering from what would be called late coeliac rickets, and the same affection has persisted until his death. The rickets in coeliac disease is of the variety with low calcium in the serum (Parsons, 1932), and the osteomalacia in this patient was of the same type. Coeliac rickets, like the osteomalacia in this adult, is associated with osteoporosis. In the bones examined microscopically in this case there is no evidence of excessive lacunar resorption, so that the porosis appears to be due to deficient osteogenesis, that is to say, deficient osteoblastic activity. Porosis due to deficient osteoblastic activity is a characteristic of Barlow's disease and of the rickets of newly born infants of women in China who suffer from osteomalacia owing to a grossly deficient diet (Maxwell, Hu, and Turnbull, 1932). The porosis of hunger osteomalacia appears to be similar. Deficient osteogenesis is, therefore, to be expected in a disease which is characterized by deficient utilization of various constituents of the food. Coeliac disease is associated with a general arrest of development that did not escape the observation of Gee (1888). The fragile atrophic long bones in coeliac rickets not infrequently show in radiograms the cross striations (Parsons, 1932) which Harris (1931) has shown to be due to periods of arrested growth. Deficient osteoblastic activity may well be one expression of this general arrest of development, although the striae in the bones show that at any rate some osteoblastic activity continues whilst endochondral ossification is arrested. Deficient osteoblastic activity appeared to be the only explanation of the porosis in the bones in this case. In the portion of tibia excised in Case 12, however, active lacunar resorption was in excess of the normal. An excessive lacunar resorption of bone to mobilize calcium for the blood would be likely to occur in a disease in which there is a deficient absorption or retention of calcium salts. It is possible, therefore, that both deficient osteogenesis and excessive lacunar resorption may play a part in the osteoporosis of coeliac disease. (H. M. T.)

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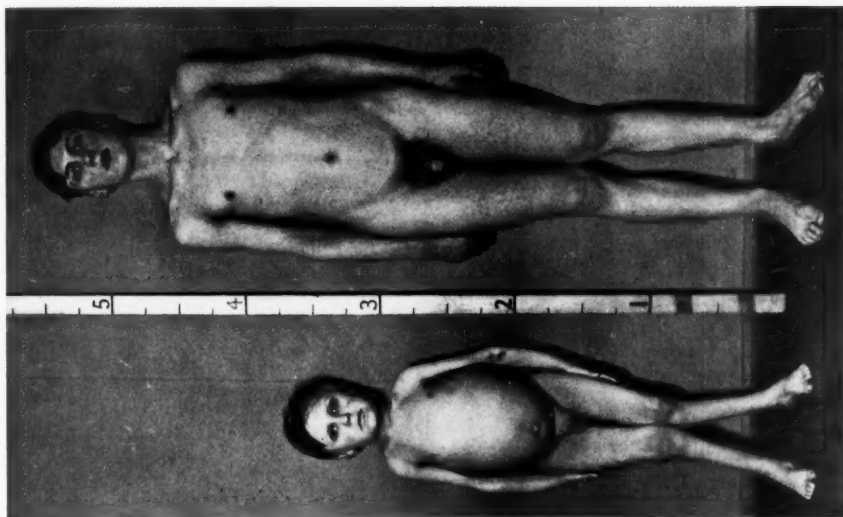


FIG. 2. Case 14. Photograph at 16 with control of the same age showing infantilism, genu valgum, and distended abdomen



FIG. 1. Case 5. To show condition at age of 58



FIG. 3. Case 10. Defective growth of hair



FIG. 4. Case 8. Pellagra-like skin eruption on right lower limb



FIG. 5. Case 2. Clubbing of fingers—skin eruption





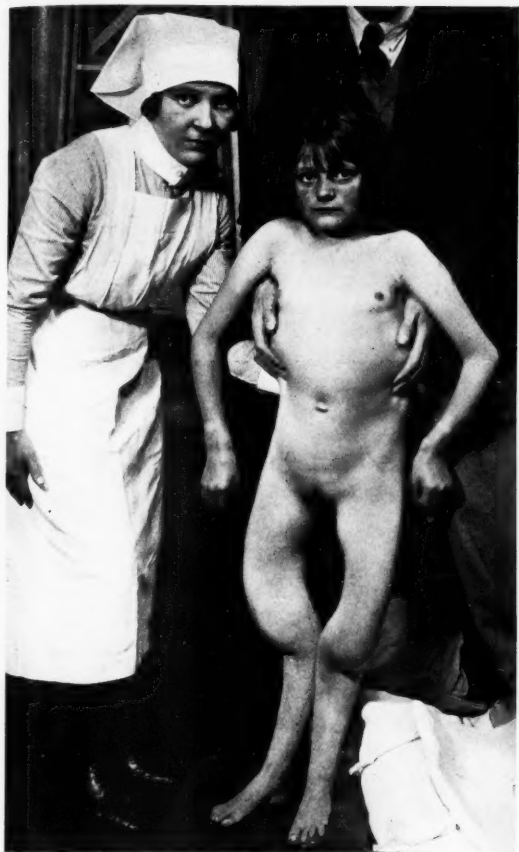


FIG. 6. Case 3. Gross deformities of bones—enlargement of lower thorax

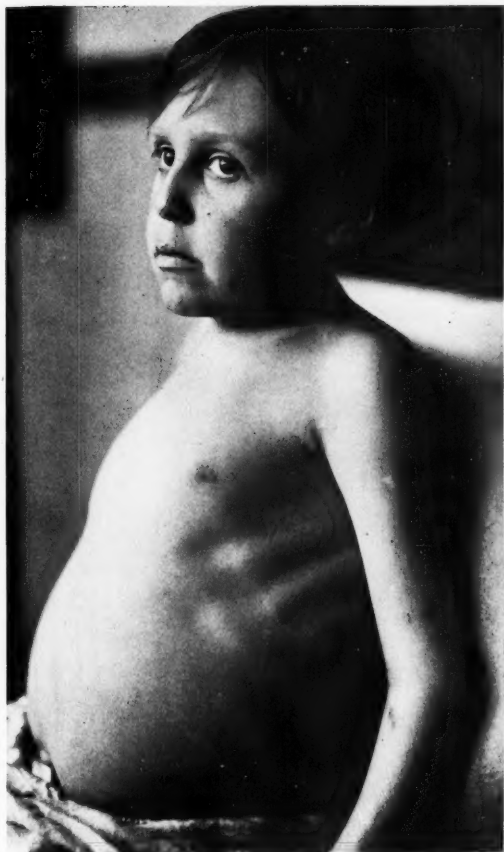


FIG. 7. Case 14. Rickety rosary and distended abdomen



FIG. 8. Case 1. Bossing of wrists





FIG. 9. Case 5. Radiogram showing gross deformity of pelvis and femora



FIG. 10. Case 9. Osteomalacia: gross deformity with beaking of pelvis

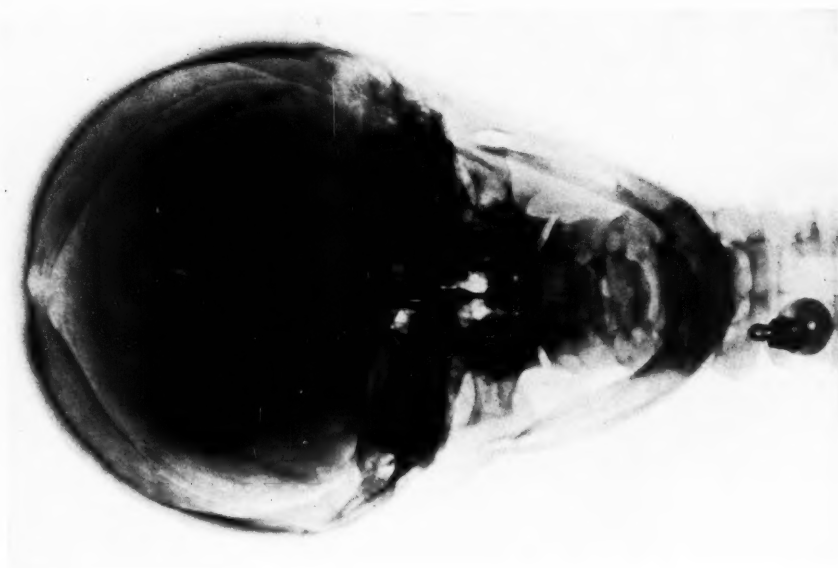


Fig. 11 B. Case 6. Radiogram of skull to show thickening of calvaria



Fig. 11 A. Case 6. Thickening of calvaria and enlargement of malar bones

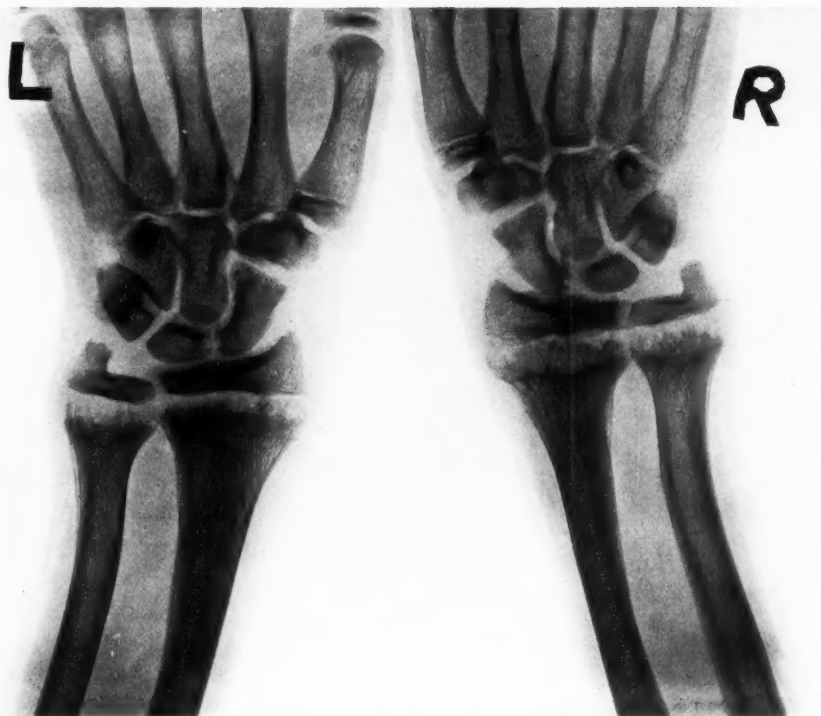


FIG. 12. Case 1. Radiogram showing osteoporosis and rickets



FIG. 13. Case 13. Radiogram of hand with control showing osteoporosis and delayed union of epiphyses



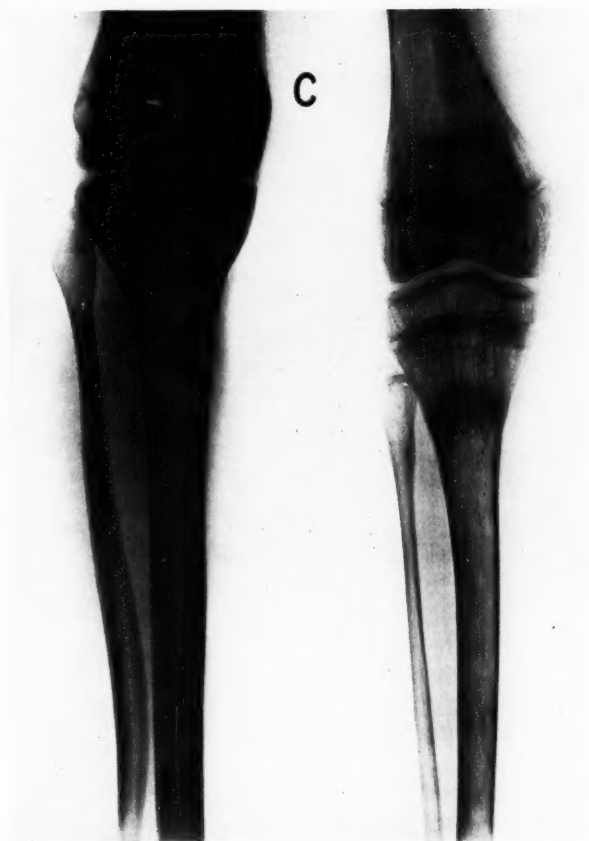


FIG. 14. Case 13. Radiogram of tibia with control to show osteoporosis and healing fractures



FIG. 15. Case 9. Opacities in the lens as seen with the slit-lamp
(Reproduced by permission of THE LANCET)





a



b



c



d

FIG. 16. Case 3. (*a*) Redundant loop of pelvic colon. (*b*) Descending and transverse colons after introduction of 4 pints of barium sulphate. (*c*) Same after introduction of 7 pints. (*d*) Outline of colon showing redundant loops whilst emptying

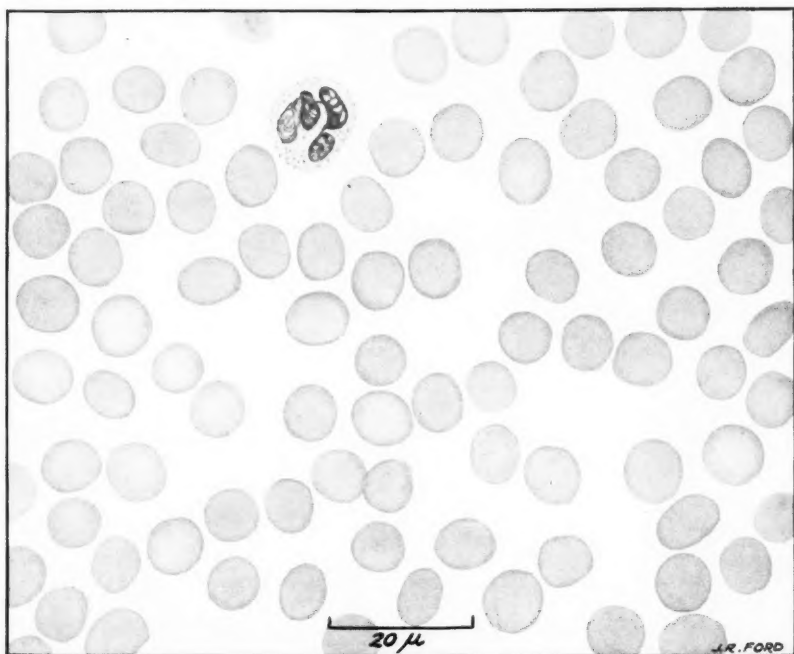


Fig. 17A.—Normal blood film. Red blood cells 4,580,000 per c. mm., Hb. 94%, C.I. 1.03, M.D. 7.3655 μ, V. 5.88%. Jenner stain.

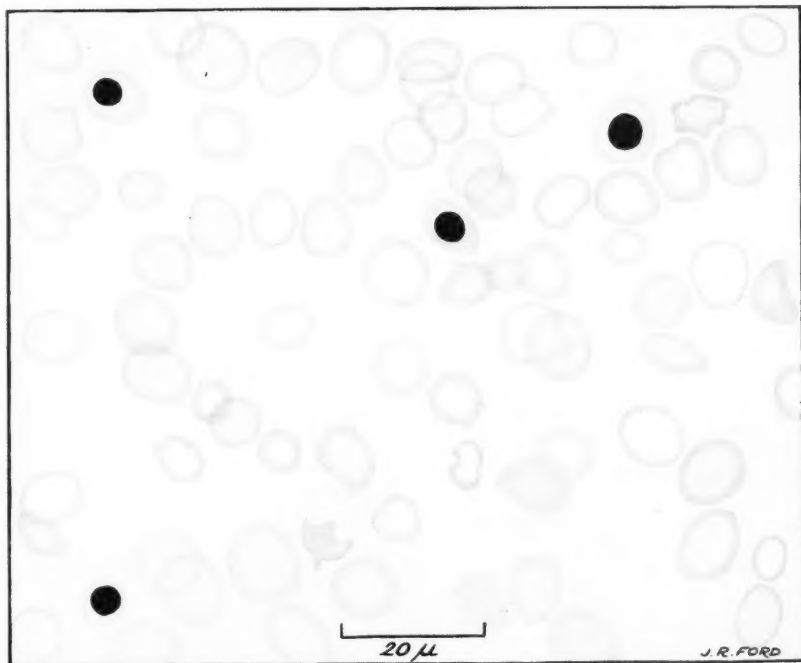


Fig. 17B.—Blood film from a case of erythroblastic anemia (Case 2). Red blood cells 3,600,000 per c. mm., Hb. 40%, C.I. 0.55, M.D. 7.6595 μ, V. 15.19%, 23.2% megalocytosis, 3.6% microcytosis. Note the nucleated red cells and large pale ring-like red cells. Jenner stain.

PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

TWENTY-SIXTH ANNUAL GENERAL MEETING

THE TWENTY-SIXTH ANNUAL GENERAL MEETING was held at Dublin on Friday and Saturday, May 13 and 14, 1932. The meeting on Friday was held in the Physics Theatre, Trinity College, and on Saturday in the Physics Theatre, National University. The Attendance Book for the Meeting was signed by 98 members. The proceedings began at 10 a.m.

The President, Professor A. J. Hall, was in the Chair.

The *Minutes* of the last Annual Meeting having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

Presentation of the Treasurer's Accounts. Dr. Morley Fletcher, Treasurer, presented the Annual Accounts which were adopted. They showed a balance of £139 14s. 7d. Dr. Fletcher explained that the expenses for the *Quarterly Journal of Medicine* were exceptional last year owing to the publication of an Index for the previous ten years.

Selection of Place of Meeting for 1933. A letter was read from Dr. Ivy Mackenzie on behalf of the local members, inviting the Association to meet at Glasgow. The invitation was cordially accepted. Invitations had also been received from Leeds and Manchester.

Election of Officers

President. Professor T. Gillman Moorhead was elected President for 1932-3. On his election he took the Chair, and expressed the thanks of the Association to the retiring President for his services during the past year.

Election of Honorary Member, Officers, Members of the Executive Committee, Extra-ordinary Members, and Ordinary Members followed :

Treasurer. Dr. H. Morley Fletcher.

Secretary. Dr. H. Letheby Tidy.

Members for England :

Professor T. Beattie.
Dr. M. A. Cassidy.
Dr. J. G. Emanuel.
Dr. A. E. Naish.
Dr. H. Thursfield.
Dr. R. A. Young.

Members for Scotland :

Dr. D. Campbell.
Dr. J. Eason.
Dr. Ivy Mackenzie.

Members for Ireland :

Dr. J. C. Rankin.
Dr. R. J. Rowlette.
Professor V. M. Synge.

As Extra-ordinary Members :

Dr. J. B. M. Anderson.
Dr. W. Bain.
Dr. C. O. Hawthorne.
Dr. G. R. Murray.

As Honorary Member :

Professor A. J. Hall (President 1931-2).

As Ordinary members :

Richard Sydney Allison, M.D., Assistant Physician, Royal Victoria Hospital, Belfast.
 Geoffrey Bewley, M.D., Physician, Adelaide Hospital, Dublin.

John Craig, M.B., Assistant Physician, Royal Aberdeen Hospital for Sick Children.

Macdonald Critchley, M.D., Assistant Physician, National Hospital, Queen Square.

Edward Revill Cullinan, M.D., Assistant Physician, Woolwich Memorial Hospital.

Leslie Cunningham, M.B., Assistant Physician, David Lewis Northern Hospital, Liverpool.

Daniel Thomas Davies, M.D., Assistant Physician, Royal Free Hospital.

Andrew Rae Gilchrist, M.B., Assistant Physician, Royal Infirmary, Edinburgh.

Richard Anderson Hickling, M.D., Assistant Physician, Charing Cross Hospital.

Bernard Edward Schlesinger, M.D., Physician, Hospital for Sick Children, Great Ormond Street.

Quarterly Journal of Medicine.

(a) Sir Humphry Rolleston's resignation as Editor was received with great regret. He had held this position since the commencement of the Journal. A hearty vote of thanks to him was passed for his services.

(b) Appointment of new Editor. The Board of Editors had nominated Dr. J. A. Ryle. The Meeting unanimously accepted the recommendation of the Executive Committee that Dr. Ryle should be appointed.

(c) Commencement of New Series. The Clarendon Press had urged upon the Board of Editors that the numbering of the Journal should be altered from January 1932, to New Series, Volume I, instead of continuing as Volume XXV. The Press had recently circularized a large number of libraries and were hoping for new subscribers. They considered that if a new series was commenced, librarians might subscribe to the Journal though they would not face providing back numbers. The decision had to be made without delay as the new number was already in the press. The Board of Editors consequently gave their consent after considerable hesitation. The Committee recognized the position in which the Board of Editors had been placed, and in the circumstances had agreed to their action. The Meeting endorsed the action of the Executive Committee and of the Board of Editors.

Deaths of Past Presidents. Before proceeding to the Scientific Business, the President referred sympathetically to the deaths of Professor J. A. Lindsay and Sir David Drummond.

SCIENTIFIC BUSINESS

*Friday Morning**1. Communications on the Use of Concentrated Serum (Felton's) in Pneumonia.*

(i) DR. R. A. O'BRIEN (introduced) on *Methods of Preparation*. In the League of Nations method of testing, serum and culture are mixed and, five minutes later, injected intraperitoneally into mice. By injecting dead culture twice a week into horses, Type I antiserum had been obtained of value 5-10 times the value of Felton standard, i.e. 1,000-2,000 'units' per c.c. The process of concentration of the 'Felton fraction' was described. To test for 'chill producing substance' the speaker found dogs unsatisfactory; he tested each batch by intravenous injection into mice. Evidence for the utility of Type II serum was weak. The Rockefeller Group treated 400 patients (Type I) with a 10 per cent. mortality, while the mortality with the concentrated serum was 20 per cent.

(ii) DRS. JOHN COWAN, A. W. HARRINGTON, ROBERT CRUIKSHANK (introduced), D. P. CUTHBERTSON (introduced), and JOHN FLEMING (introduced) reported the results obtained in a series of 155 cases of pneumonia treated with Felton's serum. 22 patients died, a mortality of 14 per cent. In an earlier series of 856 cases, treated by them without serum, 158 patients died, a mortality of 18 per cent. Felton's serum is only applicable to cases due to Types I and II pneumococci, but nearly three-fourths of the cases in Glasgow were due to one of these types. (Of 737 cases typed in Glasgow, 37 per cent. were Type I; 34 per cent. were Type II; 4 per cent. were Type III; 23 per cent. were Type 'x'.)

132 typed cases were given serum on admission to hospital.

44 cases were due to Type I; of whom 2 died.

45 " " " II; " " 8 "

6 " " " III; " " 5 "

37 " " " 'x'; " " 4 "

The mortality in a contemporary series of 589 cases, treated without serum—in various hospitals in Glasgow—was: 10 per cent. in Type I; 17 per cent. in Type II; 29 per cent. in Type III; and 9 per cent. in Type 'x'.

The number of cases treated with serum is small, but the results suggest that the use of serum has lessened the mortality of Type I cases by half or more, but has little effect on the mortality of Type II cases. The dose of serum in Type II cases was perhaps insufficient.

(iii) DR. RICHARD ARMSTRONG demonstrated by lantern diagrams that antibodies made their appearance in the blood of the experimental animal, inoculated with killed pneumococcal vaccine, as early as the third day after inoculation. He showed that serum immunity was seldom demonstrable in the untreated case of adult lobar pneumonia before the fifth day of illness so that crisis often occurred later, on the seventh day, the tenth day, or was still further delayed. Passive immunization by the intravenous injection of anti-pneumococcal serum concentrate seemed to help to eliminate the pneumococci and their products. The effect of serum treatment was conservative therefore, so that the wave of natural immunity was free to appear on the fifth day and crisis followed. In cases of lobar pneumonia of moderate severity it was possible, by flooding the circulation with the concentrate, to produce a marked improvement with fall of temperature earlier than the fifth day.

Tabular summaries of the results of treatment of alternate cases were shown. Contrasting the outcome in 50 treated cases of Type I and Type II infection with 50 controls, the day of crisis was advanced from 24 to 48 hours. The number of cases ending by lysis was reduced; convalescence was accelerated. The incidence of complications was unaltered.

(iv) DR. D. MURRAY LYON stated that in order to get as homogeneous a series as possible all cases under 20 and over 60 years of age were excluded, and serum was not given to cases admitted to hospital after the fifth day. Alternate admissions were taken as controls. Acceptable proof that a remedy has had a beneficial action would be a reduction in mortality or a definite modification of the course and the severity of the disease.

Case mortality: in Type I cases, one death occurred amongst 22 cases who received serum (4.5 per cent.), as compared with a death-rate of 17.3 per cent. in the non-serum cases. In Type II cases, the death-rate was 30.8 per cent., and 30.1 per cent. in the serum and the non-serum cases respectively. These figures are of little value because of the small numbers.

Influence on course of the disease: of Type I cases, 52.5 per cent. of those who had serum had a crisis by the fifth day, as against 18.5 per cent. of the controls. The corresponding figures for Type II cases, were 40.8 per cent., and 20.7 per cent. There was a certain amount of evidence that the clearing up of the local signs was not hastened, even where an early crisis had been produced. Early serum reactions of an asthma-like character were seen in 3 patients out of 61, and 4 others complained of joint pains, &c., about ten days after the serum had been given.

The impression of all those in Edinburgh who had used the serum was that it was distinctly useful, especially in cases of Type I infection, if given early enough in the course of the disease.

(v) PROFESSOR L. S. P. DAVIDSON. During the period October 1930 to April 1932, 161 cases of lobar pneumonia were admitted to hospital: 27 cases (16.7 per cent.) died. The distribution of the 161 cases into types, with their corresponding mortality figures, is shown in Table I. The effects of serum treatment are indicated in Table II. If patients below the age of 20 and above the age of 60, as well as those who came into hospital after the fifth day of the illness are eliminated, the figures are even more striking. There were 17 cases of Type I pneumonia treated with serum, with no deaths, and 13 control cases, with four deaths. Table III gives the percentage distribution and mortality of cases with positive blood cultures. The effects of serum therapy can be judged, not only by mortality figures, but by improvement in the clinical condition of the patient, and by the shortening of the duration of the disease. The average time of crisis after admission was 2.7 days in the treated series, as

compared with 4 days in the control series. While 50 per cent. of the treated cases had a crisis within 48 hours of admission, this occurred in only 17 per cent. of the untreated.

Conclusions. The figures submitted are too small to be of statistical value, but any evidence available supports the view that in Type I pneumonia serum definitely lowers the death-rate. In Type II cases serum had no effect on the mortality figures, and it is suggested that this is due to insufficient dosage. Serum therapy had undoubted beneficial effects on the symptomatology and course of the disease.

TABLE I. *Distribution into Types.*

	No. of Cases.	Deaths.	Mortality per cent.
Type I	38	4	10.5
" II	33	5	15.1
" III	32	9	28
" 'x'	56	8	14
Type 'x'			
(Subsequently Type I)	1	0	0
Type 'x'			
(Subsequently Type II)	1	1	100

TABLE II. *Comparison of Treated and Untreated Cases.*

	No. of Cases.	Mortality per cent.
Type I Serum	22	<div> <div>1 died</div> <div>21 cured</div> </div> 4.5
Controls	16	<div> <div>3 died</div> <div>13 cured</div> </div> 18.7
Type II Serum	14	<div> <div>2 died</div> <div>12 cured</div> </div> 14.3
Controls	19	<div> <div>3 died</div> <div>16 cured</div> </div> 15.8
Types I and II	Treated 36	3 died 9.3
	Controls 35	6 " 17.1

TABLE III. *Blood Cultures.*

Total cases: 161.

Blood cultures: positive 19—11.8 per cent.

	No. of Cases.	Deaths.	Deaths per cent.
Type I	4	1	25
" II	5	2	40
" III	7	3	42.8
" 'x'	3	3	100
Total	19	9	47.3

DR. McNEE stated that the mortality of pneumonia in the United States of America was 50 per cent. He suggested that this might be due to passage through the coloured races. Radiographs showed that pneumonia usually started at the hilum.

DRS. MOORE, BURRELL, AND GASKELL also discussed the communications.

2. DR. F. C. PURSER related a *Case of Spreading Ulceration of the Skin following Appendicectomy*. Operation for appendicitis with abscess formation on February 5, 1929. The deeper layers of the abdominal wound healed satisfactorily, but ulceration of the skin and subcutaneous tissue began and spread widely. The ulceration involved the greater part of the abdomen surrounding the navel but leaving this intact. The sloughing ceased to spread in November 1930, and no area could be found uncovered by epithelium at the end of December 1930. Bacteriological examination revealed at first only *Streptococci* and *Staphylococcus aureus*. In October 1929, diphtheroids were

also found, and constantly afterwards. (The case was thought originally to be one of extra-facial diphtheria.) No streptothrix was ever found. Treatment of every sort was ineffective.

3. DR. HENRY COHEN communicated the *Results of the Treatment of Narcolepsy with Ephedrine*. After a preliminary statement of the factors which led to the use of ephedrine he detailed the results of 9 cases personally observed in which considerable symptomatic relief of both narcoleptic and cataleptic attacks had followed its administration.

DR. GORDON HOLMES described cases which he had treated personally.

2 p.m. to 3 p.m.

Demonstrations of Clinical Cases and Pathological Specimens at the Royal College of Physicians.

Demonstrations by Dr. R. R. Armstrong of Direct Typing of Pneumococci.

Exhibition of rare Medical Books by Dr. T. P. C. Kirkpatrick.

3 p.m. Afternoon Session

1. DR. E. P. POULTON on *Construction and Management of an Oxygen Bed Tent*. The new principles used in the type of oxygen bed tent demonstrated were: (1) Cooling and drying were effected by ice-containing tins let in through the roof of the tent. (2) Cecil and Plummer's Injector was used for ventilation, but arrangements were made so that the rate of flow and the oxygen in the air could be adjusted. (3) Shackle's clinical oxygen pipette and the Author's clinical CO₂ pipette were devised to enable a nurse without training to determine the composition of the air inside the tent.

2. DR. GEOFFREY EVANS on *Local Disease as a Factor determining the Path of a Viscero-sensory Reflex*. He reported three cases in which the radiation of visceral pain due to organic disease was determined by organic disease elsewhere. In the first case, intestinal pain associated with diverticulosis of the transverse colon radiated to the precordium on account of organic heart disease. In the second case, the pain of organic heart disease was felt in the back of the neck on account of cervical arthritis. Although the heart disease is progressive in this case as judged by electrocardiogram records, the pain in the neck has been cured by local treatment for the arthritis. In the third case, the pain of gastric dyspepsia was referred to the right shoulder-joint on account of arthritis in this joint. On the basis of Mackenzie's theory of visceral pain Dr. Evans suggested that these cases illustrated the general principle of local disease as a factor determining the path of a viscerosensory reflex.

DRS. HURST, POULTON, ABRAHAMSON, and WILKINSON discussed the views expressed.

3. DR. A. R. PARSONS discussed two cases. (a) *Spontaneous Pneumothorax*. He reported a case in which the patient was suddenly seized with severe pain in the right side of the chest. He came to hospital a week after onset of illness with the usual signs of right pneumothorax. Physical signs soon disappeared, and a second X-ray examination ten days after the first, showed that the lung had expanded to three-quarters of normal. A few weeks later the lung had completely expanded. Patient left hospital quite well, and has remained so.

(b) *Rare Intrathoracic Tumour*. On routine examination of a man aged 60 years who was suffering from acute influenza, an area of dullness starting at the level of the second left costal cartilage and extending outwards for 3 and 4 inches was detected. X-ray examination showed a large ovoid tumour on the left side springing apparently from the hilum and with a definite pedicle. The shadow was uniform, but was mottled by some opacities due to calcification within the tumour or on its surface. Differential diagnosis was between dermoid or hydatid cyst. The latter view was taken, and, if correct, this case appears to be the only example of an intrathoracic hydatid recorded in Ireland where hydatids are very rare.

DR. A. P. THOMSON suggested that the pulmonary tumour was a calcified dermoid, and PROFESSOR T. K. MONRO suggested a neoplasm.

DRS. BURRELL and LANGDON BROWN also spoke.

4. DR. L. ABRAHAMSON gave two communications. (a) *A Case of Bilateral Pneumothorax*. The patient, male, aged 35, was seen first on March 13, 1931. Ten days previously he had experienced pain in the left chest, followed by breathlessness, but was able

to carry on his occupation. Examination showed signs of bilateral pneumothorax, and this was confirmed by X-ray examination. Some hours later, he suddenly collapsed. Air was removed from each side of the chest and improvement occurred. Six days later urgent symptoms reappeared and aspiration of air was again performed. Attachment of the needle to a manometer showed that on the right side the opening was valvular, and it was found impossible to reduce the air pressure on this side below +12. From this time, improvement was maintained and the left side cleared completely. The right-sided pneumothorax, however, persisted and was still present at the date of the communication. In spite of this, the patient was able to carry on arduous business and to indulge in moderate exercise.

(b) *Eventration of the Diaphragm.* Dr. Abrahamson defined this as a general expansion of one half of the diaphragm, allowing the abdominal viscera to be displaced upwards into the thoracic cavity. Many facts supported a congenital origin. In the vast majority of cases, the left side of the diaphragm was involved: in some of the right-sided cases, congenital non-rotation of the stomach was associated. Most cases occurred in males. Symptoms were frequently absent. When present, they consisted of gastro-intestinal disturbance, dyspnoea, loss of weight, and cough.

Dr. BURRELL said he believed that spontaneous pneumothorax is not due to tuberculosis and is not followed by it. It is probably caused by rupture of a single bulla.

Drs. COLE, HAY, NAISH, and PLATT mentioned similar cases.

5. Dr. E. T. FREEMAN discussed *The Treatment of Pleural Effusion*. The ideal method should cause no danger or distress to the patient, should ensure as far as possible against the spread of pulmonary disease, and should aim at total emptying of the chest to prevent basal fibrosis. This can be done by gas replacement. An apparatus simplifying the technique of gas replacement was demonstrated. The basis of this is the three-way blood transfusion syringe known as the 'Rotanda', made by Haselmeier of Stuttgart. Fluid is aspirated from the chest, and through the same trocar air or oxygen is pumped in. The pressure is taken at the close by connecting a manometer to the end of the trocar by an ordinary adapter. This method was shown to be single-handed and to be within the capabilities of every one who can use a syringe.

6. PROFESSOR V. M. SYNGE and Dr. T. G. HARDMAN (introduced) on *A Case of Intracranial Pneumatocele*. A man, aged 27, complained of headache and vomiting in September 1930. After a few weeks the right arm and leg became weak. The symptoms disappeared but returned in February 1931. The reflexes in the right arm and leg were exaggerated, Babinski was present. X-ray showed a large air-filled cyst in the left cerebral hemisphere and a large osteoma in region of frontal sinus, the air having apparently entered through a breach in the cribriform plate. The air absorbed, hemiplegia disappeared, and patient remains well.

The Annual Dinner was held at the Royal College of Physicians. The President, Professor T. Gillman Moorhead, was in the Chair. The official guests included Mr. E. J. Gwynn, Provost of Trinity College, Mr. R. A. Stoney, President of the Royal College of Surgeons, and Sir John W. Moore. 102 members and guests were present.

Saturday Morning

1. PROFESSOR E. J. CONWAY (introduced) on *The Numerical Expression of Renal Function*. He discussed various mathematical formulae.

2. Dr. HUGH BARBER on *The Life History of the Renal Dwarf*. In 1883, the association of 'late rickets' with albuminuria was noted; but Morley Fletcher, in 1911, first recorded great want of development and bone deformities in children with interstitial nephritis. Since 1912, twenty of these cases have been under observation at the Derbyshire Royal Infirmary. The morbid anatomy in most cases is that of primary interstitial nephritis, beginning early in life. The bone deformities commence about puberty, although sometimes sooner. They are preceded by thirst, polyuria, and want of development; but these features may be too slight to be noted, and the first stage of renal dwarfism is easily overlooked. In the 'late rickets', or renal rickets stage, the deformities, radiographic changes, low specific gravity urine with trace of albumin, are characteristic. The blood urea is high, with low calcium and raised phosphates. The cardiovascular changes are slight. The blood-pressure is usually normal. Death usually occurs from uraemia in this stage between 14 and 18 years of age. But a few live to a stage when the epiphyses are joined. One child, aged 3 years,

was under observation for thirst and polyuria, the late rickets stage developed at 12 years, the epiphyses were united at 20 years, and she is alive aged 26 years. Renal infantilism is too narrow a term—the girls may have menstrual periods. Renal rickets only describes one stage—the most characteristic. A suitable label for the whole clinical course is renal dwarfism; because all cases show considerable want of development, and the other evidences of kidney disease may not be sufficiently noticeable to bring the child under observation.

DR. PARKES WEBER referred to several points.

3. DR. ROBERT PLATT gave a communication on *Sepsis and Nephritis*. He discussed the results of removal of septic foci in the treatment of nephritis. 102 cases of nephritis (including all forms except chronic nephritis) admitted to the Royal Infirmary, Sheffield, between the years 1924 and 1929, were followed up in 1932, and classified according to whether septic foci were (1) present and not removed, (2) not found, or (3) found and removed. Owing to the wide variations in the natural severity and course of nephritis, it was decided to limit the investigation to cases commencing acutely which had shown a definite remission of symptoms after the acute stage, i.e. disappearance of oedema and marked diminution of albuminuria. Out of 87 such cases, in 41 septic foci were still present, and of these 20 were apparently cured of nephritis, 7 were doubtful, 3 had developed chronic nephritis, 2 had died, and in 9 cases nephritic symptoms had recurred. In 27 cases, septic foci were not found on re-examination, and in some of these it is not known whether sepsis was present at the commencement of the disease. 10 of these cases are cured, 4 doubtful, 3 have chronic nephritis, 3 have died, and in 7 there has been recurrence. The remaining 19 cases have had septic foci successfully removed, and are all well and apparently cured. The results therefore appear to show that the removal of septic foci, where present, has a favourable influence on the course of acute nephritis.

This communication was discussed by DRs. McNEE, TIDY, EVANS, A. P. THOMSON, BOXWELL, and PARKES WEBER.

DR. PLATT replied.

4. DR. A. GEOFFREY THOMPSON (introduced) described investigations upon *A Case of Pure Acute Uraemia* in a boy, following the surgical removal of a solitary kidney which had been destroyed by trauma. The clinical and biochemical features of the case were described. It was regarded as of considerable importance on account of the complete absence of all complicating extrarenal factors, and it was suggested that the findings might throw some light upon the pathogenesis of certain features of so-called 'chronic uraemia' occurring in the course of nephritis and gross lesions of the kidney.

DR. POULTON was of the opinion that the liver was affected in this case.

DR. PLATT also spoke.

5. PROFESSOR L. S. P. DAVIDSON and ALEXANDER CALDER (introduced) discussed *The Diagnosis of Carcinoma of the Stomach, with special Reference to Lactic Acid*. They stated the following conclusions from a study of the gastric contents of 80 cases of cancer of the stomach, compared with a control series of approximately 1,000 test meals from normal persons and from patients suffering from a great variety of diseases.

(1) Lactic acid has no specific relationship to cancer of the stomach, for the following reasons: (a) It belongs to the fermentative type, as shown by chemical and polarimetric investigations and by quantitative bacteriological methods which reveal a correlation between the amount of lactic acid and the number of lacto bacilli present in the gastric contents. (b) Lactic acid may occur in non-malignant disease of the stomach, and be absent in cases of gastric cancer. (c) Lactic acid may result from extra gastric causes and arise in extra gastric situations.

(2) Lactic acid occurs in 50 per cent. or more of cases of gastric cancer, and in only approximately 5 per cent. of cases suffering from all other diseases combined.

(3) Lactic acid production depends on the simultaneous occurrence in the stomach of a suitable hydrogen-ion concentration and a delay in the gastric emptying time. A combination of these two factors is found ten times more frequently in cancer of the stomach than in all other gastric diseases.

(4) A positive lactic acid test, while not pathognomonic of cancer, is unquestionably a helpful diagnostic sign. All patients in whom lactic acid can be demonstrated by qualitative tests should be regarded as potential sufferers from gastric cancer till

the diagnosis is disproved by careful radiological investigation, and an alternative explanation for the achlorhydria and stasis substituted.

DR. HURST emphasized the fact that the diagnosis of cancer from ulcer could be based on the persistence of occult blood.

DR. DAVIDSON in reply believed that this test would often fail.

6. DR. A. P. THOMSON made a contribution to *The Study of Intermittent Headache*. He described 25 cases of intermittent headache in women most marked at menstruation. Radiological abnormalities were present in the sella turcica in 17 of these, the most common being calcification of the interclinoid ligaments. Considerable relief followed the use of the ovarian follicular hormone in the week prior to menstruation. The series included 2 cases of inherited menstrual headache in which radiographs of the mothers showed the same X-ray abnormality as the daughters. An examination of the normal anatomy of the sella turcica showed that in the great majority the current anatomical description of the diaphragma sellae was incorrect.

DR. GORDON HOLMES expressed great interest in this communication.

2 p.m. to 3 p.m.

Demonstration of Clinical Cases and Pathological Specimens at the Royal College of Physicians.

3 p.m. Afternoon Session

1. DRS. J. W. MCNEE and C. PRICE-JONES (introduced) reported the *Occurrence of Pernicious (Addisonian) Anaemia in Identical Female Twins*, aged 61. Price-Jones curves were typical, and achlorhydria was found in each. These cases appear to be unique in medical literature. Pernicious anaemia in identical twins, aged 81 years, has been reported from Sweden, but a study of the case histories shows clearly that an error in diagnosis was made.

DRS. HURST, ABRAHAMSON, and NATTRASS discussed these observations.

2. DR. F. PARKES WEBER narrated the *Sequel to the Case of Apparently Aplastic Anaemia* in a man, aged 31 years, communicated to the Association at the Annual Meeting of 1931. The patient was kept alive by repeated blood transfusions, which in July brought up his erythrocyte count to over $4\frac{1}{2}$ millions; and at the time he felt fairly well. But some parosteal swellings developed over the ribs, sternum, and upper jaw. Very severe haemorrhagic symptoms led to the patient's death in September, and the post-mortem examination proved that the disease was really a persistently leucopenic form of aleukaemic myelosis.

DRS. TIDY and DAVIDSON took part in the discussion.

3. DR. L. J. WITTS on *The Hereditary Form of Purpura Haemorrhagica (Type Glanzmann)*. He described three different families in which he had observed the inheritance of purpura haemorrhagica. In two of the families the symptoms were associated with a shortage of platelets, but in the third family the number of platelets was normal. The condition affected males and females and tended to become less severe in later life.

Similar cases were mentioned by DRS. PARKES WEBER and MCNEE.

4. DR. J. F. GASKELL described *The Condition found in the Liver in a Case of Catarrhal Jaundice*. A girl aged 5 years died from uncontrollable haemorrhage from the site of the removal of the tonsils and adenoids. The operation was performed the day before an attack of catarrhal jaundice, the patient dying on the third day of this disease. The condition found was a true hepatitis; there was no evidence of duct obstruction.

PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

TWENTY-FIFTH ANNUAL GENERAL MEETING

THE TWENTY-FIFTH ANNUAL GENERAL MEETING was held in Sheffield on Friday and Saturday, May 22 and 23, 1931, in the Mappin Hall, Applied Science Department of the University. The Attendance Book for the Meeting was signed by 130 members. The proceedings began at 10 a.m.

The President, Sir William Hale-White, was in the Chair.

The Minutes of the last Annual Meeting having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

Election of Officers

President. Professor A. J. Hall was elected President for 1931-32. On his election he took the Chair and expressed the thanks of the Association to the retiring President for his services during the past year.

Election of Officers, members of the Executive Committee, Extra-ordinary members, and Ordinary members followed.

President. Professor A. J. Hall.

Treasurer. Dr. H. Morley Fletcher.

Secretary. Dr. H. Letheby Tidy.

Members for England :

Professor T. Beattie.
Dr. W. Langdon Brown.
Dr. J. G. Emanuel.
Dr. Gordon M. Holmes.
Dr. A. E. Naish.
Dr. R. A. Young.

Members for Scotland :

Dr. A. Greig Anderson.
Dr. J. Eason.
Dr. Ivy Mackenzie.

Members for Ireland :

Sir Thomas Houston.
Dr. R. J. Rowlette.
Professor V. M. Synge.

As Extra-ordinary Members :

Sir Ashley W. Mackintosh, M.D.
Dr. Harry Campbell.
Dr. R. A. Fleming.
Dr. W. Hunter, C.B.
Dr. A. F. Voelcker.

Ordinary members :

George Ernest Beaumont, M.D., Physician, Middlesex Hospital.

Edward A. Carmichael, M.B., Assistant Physician, National Hospital for Nervous Diseases, Queen Square.

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- William Tregonwell Collier, M.D., Assistant Physician, Radcliffe Infirmary, Oxford.
Maurice Davidson, M.D., Physician, Brompton Hospital for Consumption.
Arthur Cecil Hampson, M.D., Assistant Physician, Guy's Hospital.
Charles F. Harris, M.D., Physician, Children's Department, St. Bartholomew's Hospital.
Thomas Cecil Hunt, M.D., Assistant Physician, St. Mary's Hospital.
James Maxwell, M.D., Chief Assistant, Medical Unit, St. Bartholomew's Hospital.
Robert Henry Micks, M.D., Physician, Sir Patrick Dun's Hospital, Dublin.
Arthur Arnold Osman, M.R.C.S., Clinical Research Fellow, Guy's Hospital.
James K. Slater, M.B., Assistant Physician, Royal Infirmary, Edinburgh.
David Smith, M.D., Senior Assistant Physician, Royal Infirmary, Glasgow.

Presentation of Treasurer's Accounts. Dr. Morley Fletcher (Treasurer) presented the Annual Accounts which were adopted. They showed a balance of £301 12s. 9d.

Selection of Place of Meeting for 1932. A letter was read from Professor Moorhead inviting the Association to meet in Dublin. The invitation was cordially accepted.

Before proceeding to Scientific Business, the President referred to the deaths of Sir Byrom Bramwell and Professor Glynn.

SCIENTIFIC BUSINESS

Friday Morning

1. DR. E. F. SKINNER ON *Examination of the Cerebrospinal Fluid with Ultra-violet Light*. The passage of ultra-violet light waves was suggested as a possible method of revealing variations in the cerebrospinal fluid, and a series of examinations have been made, using tungsten and copper as a source of ultra-violet waves. The alterations in the normal spectrum which occur in certain diseases were discussed, the most marked being in tuberculous meningitis.

2. DR. E. MELLANBY discussed *The Experimental Production and Prevention of Spinal-cord Degeneration*. Degeneration of groups of fibres in the spinal cord of puppies, demonstrable by Marchi's and Weigert's methods, can be experimentally produced by feeding them on mixed diets which are rich in cereals and deficient in vitamin A. If ergot of rye be added to the same diets the degenerative processes are more intensely produced. To a less degree the addition of the germ of cereals, e.g. of wheat and rye, also increases the degenerative changes. In all cases, even when ergot is added to the food, the animals remain in good health and develop no demyelination of the cord fibres if foodstuffs containing vitamin A are eaten. Both vitamin A and carotene also bring about great improvement in the condition after it has developed. Thus it appears from this experimental work that this type of cord degeneration depends (1) on a neurotoxic action associated with ergot and possibly with cereals generally, and (2) the absence of a protective mechanism in which vitamin A and carotene play an important role. This work would appear to have a direct bearing on the aetiology and treatment of (a) convulsive ergotism in man, (b) the central nerve lesions of pellagra, and (c) lathyrism. The possibility that vitamin A played a part in subacute combined degeneration of the cord in pernicious anaemia was also alluded to. The protective action of foods rich in vitamin A and carotene against the neurotoxic agents described was so great that it seemed advisable to test these foods as therapeutic agents in all cases of spinal-cord degeneration, including general paralysis, tabes dorsalis, and disseminated sclerosis.

Dr. Yates referred to two cases of dementia paralytica which had been placed on a diet rich in vitamin A and carotene, as suggested by Dr. Mellanby, and had greatly improved.

Drs. Parkes Weber, D. Campbell, and McNee discussed this communication.

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3. DR. C. L. SUTHERLAND (introduced) gave a communication on *The Clinical Aspects of Silicosis*. Silicosis occurs in this country in workmen usually over 35 years of age, but cases may occur under that age. It may occur in young adults in the form known as acute silicosis. The condition may be latent and only appear some years after the worker has left his occupation. The length of exposure to the dust is usually from 15 to 20 years, but this depends on intensity of the exposure. The diagnosis rests on the radiological examination, the X-ray film showing a mottling of the lung substance. Symptoms may not be present at the early stage and the physical signs detected are limitation of movement, a flat note on percussion and diminution of breath sounds. As the disease progresses, the symptoms and physical signs become more pronounced. On the X-ray film the nodules tend to coalesce and later to form masses. The presence of tuberculosis in silicosis cases is detected by the sputum examination, by the physical signs, and, in the X-ray film of asymmetrical shadowing, or in some cases, denser shadows at both apices.

4. PROFESSOR M. J. STEWART (introduced) on *Observations and Experiments on Pulmonary Asbestosis*. He described the morbid anatomy from his experience of 9 cases seen at autopsy, emphasizing the diffuse character of the pulmonary fibrosis as compared with the nodular lesion in silicosis. In the later stages bronchiectasis appears, but it is exceptional for tuberculosis to be superimposed. The 'asbestosis bodies' which are formed in the lungs as a result of interaction between the asbestos fibre and the body fluids were described and their nature discussed. Exposure of guinea-pigs to ordinary factory concentrations of dust for periods ranging from 3 to 14 months has led constantly to the appearance of bodies in the lungs.

With regard to these two communications (3 and 4), Dr. L. G. Irvine (introduced) referred to occurrences of silicosis in gold mining in South Africa. Formerly there were over 800 cases a year, but this had been reduced to less than 300. Silicosis and tuberculosis are independent affections, but each modifies the other when both are present.

Drs. R. A. Young, Wilkinson, and G. Murray, joined in the discussion which followed.

5. DR. GORDON M. HOLMES on *Vascular Tumours of the Forebrain*. This communication was based on five vascular tumours of the forebrain of the cavernous haemangioma type observed during the past two years. Such tumours constitute from 2 to 3 per cent. of all intracranial growths, and as they are of long duration and present only isolated symptoms, their diagnosis is often difficult. Epileptic phenomena are frequent, and symptoms of increased intracranial pressure appear late. The chief points in their differential diagnosis are the presence of naevi on the face, or of distended vessels in the neck and scalp, tortuosity of the retinal veins and the presence of a murmur in the head heard by the patient and usually audible on direct auscultation of the skull. In the five cases described, the tumours occupied the temporo-occipital lobes of the brain and visual symptoms were therefore present.

6. DR. H. CARLILL exhibited a man whom he stated to be suffering from *Hysterical Sleeping Attacks*.

2 p.m. to 3 p.m.

Demonstration of Clinical Cases, Pathological Specimens, and Radiographs and Specimens illustrating Silicosis at the Royal Hospital.

3 p.m. Afternoon Session

1. DR. F. PARKES WEBER discussed two cases (1) *Aplastic Anaemia treated with Blood Transfusion*, and (2) *Generalized Lymphosarcoma*. The first case was that of a young man with aplastic anaemia, whose life can be maintained only by repeated blood transfusions. The second case related to that of an elderly woman who died with extraordinarily rapid generalization of a lymphosarcoma-like growth, soon after the removal of a swelling under the lower jaw by radium treatment.

These cases were discussed by Drs. Poulton, Hurst, Stanley Davidson, and Tidy.

2. DR. O. LEYTON gave a communication on *Hyperglycaemic Glycosuria Anosos*. A number of patients under observation, whose sugar tolerance tests prove that they have had hyperglycaemic glycosuria, have eaten unrestrictedly without the administration of insulin, and nevertheless have not lost any power of storing carbohydrate as demonstrated by the sugar tolerance tests. Several of these patients have been subjected to tolerance tests after a week of diet with a low carbohydrate content, and again after a week of diet rich in carbohydrate. The typical difference which occurs in the diabetic subject has been absent. During the last five years he had seen several cases in which

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the renal thresholds for dextrose have been not less than 0.19 per cent. with histories of glycosuria for periods up to 20 years, during which time restricted diets have been the exception rather than the rule, and these when submitted to the tests mentioned above failed to show anything more than hyperglycaemic glycosuria. None of these patients had any symptoms of disease.

3. PROFESSOR A. RAMSBOTTOM reported a case of *Spontaneous Hyperinsulinism*, and discussed the possible causation. The patient was a children's nurse aged 44, who in 1923 unexpectedly became sulky and self-assertive. In 1925 she took a situation where she lived largely on tinned foods and seldom had any sweets. After a few months she complained of attacks of 'shakiness' and 'faintness', but did not actually faint. Subsequently she had attacks of loss of consciousness, petit mal, and hysteria. In 1930 she was admitted into the Bradford Royal Infirmary under Dr. Eurich, and while there had attacks of loss of consciousness every day about 5 a.m. In these attacks she became very pale, sweated profusely, and had a very weak pulse. Hypoglycaemia was suspected, and an estimation of the blood-sugar gave 0.046 per cent. Glucose ($\frac{1}{2}$ lb. daily) was administered. The blood-sugar rose to a maximum of 0.064 per cent. with an appreciable improvement in the patient's condition. On February 24, 1931, she was admitted into the Manchester Royal Infirmary. The blood-pressure was 115/75, and the blood-sugar 0.046 per cent. Five days later she became stuporose. The blood-sugar was now 0.031 per cent. and fell to 0.028 in three days. She remained in coma for five days. Adrenalin 0.5 (1 in 1000) was administered subcutaneously. Her mental condition improved somewhat. The effect of the administration of adrenalin on the blood-sugar was as follows:

Blood-sugar	5 minutes after giving adrenalin	= 0.041 per cent.
" "	15 " " " "	= 0.049 " "
" "	30 " " " "	= 0.060 " "
" "	1 hour " " " "	= 0.071 " "
" "	2 " " " "	= 0.081 " "
" "	2½ " " " "	= 0.073 " "
" "	3 " " " "	= 0.065 " "

As the coma increased on the following day, 400 c.c. of a 20 per cent. solution of glucose were given intravenously, and the coma rapidly became less profound. Subsequently 1 lb. of glucose was given daily by the mouth. The condition improved and consciousness returned, but later epileptiform convulsions and hysterical fits occurred. A laparotomy was performed but the pancreas appeared normal. She is still having 1 lb. of glucose daily, but in spite of this has frequent hysterical outbursts at night, and on the whole there is little perceptible improvement in her mental condition. The actual cause of the hypoglycaemia in this case has not been determined. Possibly the islet tissue of the pancreas is increased. There is no evidence of a cerebral lesion.

Sir Humphry Rolleston suggested that the condition was due to liver deficiency.

Dr. Brain described similar cases.

Drs. Morris, Parkes Weber, and F. R. Fergusson joined in the discussion.

4. DR. H. F. MOORE on *A Clinical Study of Achlorhydria*. Fractional test-meal examination was done on 1,171 patients between January 1, 1927 and March 31, 1931; of these 256, or 21.8 per cent. had complete achlorhydria. Forty-four cases of secondary anaemia of doubtful aetiology were studied, and of these 30, or 68.1 per cent. had achlorhydria. Seventy-nine cases of diabetes mellitus were examined, and 33 of them, or 41 per cent. had achlorhydria. Forty cases of hyperthyroidism were examined, and 32, or 80 per cent. had achlorhydria. In the entire series there were 97 gastro-intestinal and 68 miscellaneous cases with achlorhydria. Two patients with diabetes mellitus, one with osteogenesis imperfecta and one with hyperthyroidism, all of whom had achlorhydria, developed the particular form of anaemia so often associated with achlorhydria. Precautions were taken to ensure that there was true achlorhydria wherever doubt existed, e.g. by washing out the stomach before the test meal or by the hypodermic injection of histamin. The following facts were observed before treatment in the 30 cases of secondary anaemia associated with achlorhydria:—Twenty-six of the cases were females and four were males, seventeen had atrophic glossitis; the average erythrocyte count was 3,600,000 and the average leucocyte count was 4,870 per cm.; the average haemoglobin content was 50 per cent., the lowest being 15 per cent. The blood bilirubin was normal in all, and in only two was the spleen palpable (one of these was a case of the Plumer Vinson syndrome). The anaemia was non-megalocytic in type. Twenty-one cases submitted themselves for a sufficient length of time to treatment by oral iron therapy with excellent results, both symptomatically and as judged

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by the blood-count. It was found that iron in the ferrous form (10 gr. per day) gave better results than in the ferric form (60 gr. per day). Hydrochloric acid in the treatment by mouth seemed to be of value only in relieving the associated gastro-intestinal symptoms. Test-meal examination of twelve successfully treated cases failed to show hydrochloric acid after the blood had been restored to normal. Liver extract for pernicious anaemia was valueless in treatment. The significance of achlorhydria and its role in producing secondary anaemia was discussed.

Dr. Hurst stated that in many cases of achlorhydria, if the stomach is washed with hydrogen peroxide, hydrochloric acid returns.

Professor Ellis also spoke.

5. DRS. ALEXANDER GOODALL and J. K. SLATER (introduced) gave a communication on *The Treatment of Cases of Disseminated Sclerosis with Liver*. Twelve cases had been long enough under treatment to show results. One, a case of ten years' duration, had regained bladder control and the speech and gait had improved within a month. Six cases unable to stand without support, became able to walk briskly. Four cases previously unfit because of weakness, tremor, bladder trouble, or mental silliness, had all returned to work, and one had made a complete recovery. The suggestion was offered that disseminated sclerosis might be a deficiency disease. The treatment employed had been the ingestion of $\frac{1}{2}$ lb. daily of lightly cooked liver. No observations with liver extracts had been made.

Dr. Gordon Holmes expressed the opinion that there was no substantial evidence at present that disseminated sclerosis is a deficiency disease.

6. PROFESSOR STANLEY DAVIDSON described *Three Cases of Macrocytic Haemolytic Anaemia*. All three cases occurred in middle-aged women whose symptoms were those of severe anaemia. The essential haematological features were as follows:—Severe oligocythaemia in two cases, the red cell count being 1,000,000 or less. Colour index over unity, varying from 1.1 to 1.5. The presence of both megaloblasts and normoblasts in the peripheral blood. The presence of marked megalocytosis as demonstrated by the Price-Jones graphical method. Normal gastric secretion. No abnormal fragility. High icterus indices, with a positive indirect van den Bergh reaction, denoting haemolytic anaemia. Waves of haemolysis recognized by a falling blood-count and increasing icterus index followed by waves of intense bone-marrow reaction, recognized by reticulocyte counts of from 25 to 50 per cent. In two of the cases massive enlargement of the spleen was present. In no case was there any enlargement of the lymphatic glands.

The relations of the group to pernicious anaemia and acholuric jaundice were discussed.

The *Annual Dinner* was held at the Victoria Hotel at 8 p.m. The President, Professor A. J. Hall, was in the Chair. The official guests included the Vice-Chancellor of the University, the Master Cutler, the Lord Mayor, the Dean of the Faculty of Medicine, the Chairman of the Royal Hospital, and the Chairman of the Royal Infirmary. 136 members and guests were present.

Saturday Morning

1. DR. C. H. MILLER discussed *The Relation of the Gall-bladder to Cardiac Pain*. Cases were referred to in which the diagnosis of cardiac pain had been made and the symptoms had been relieved after the passage of gall-stones. Personal experiences of relief of cardiac pain after cholecystectomy were given. In a series of 200 cases of gall-bladder disease, it was found that severe coronary atheroma, myocardial fibrosis and recent cardiac infarction, together, were $3\frac{1}{2}$ times as frequent as in a series of cases in which the gall-bladder was healthy. The removal of a diseased gall-bladder in cases of cardiac pain was advocated for two reasons: (1) the probability that pain would be relieved; (2) the risk was not great.

Drs. Goodall, Hurst, and other members agreed with Dr. Miller.

Dr. Hamil referred to the association of appendicitis with cholecystitis.

2. DR. A. F. HURST on *Megacolon and Eventration of the Diaphragm*. Megacolon is more common in adults than in children, although the condition has hitherto been rarely recognized except in children (so-called Hirschsprung's disease). He had seen

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25 cases: 7 boys, 1 girl, 9 men, 8 women. The condition is always acquired; it is the result of achalasia of the anal sphincter caused by degeneration of Auerbach's plexus, owing to which the sphincter remains closed instead of relaxing in the act of defaecation. The resulting obstruction leads to overaction of the pelvic colon and rectum, the muscular coats of which become hypertrophied. In spite of this, evacuation of faeces and gas is incomplete. Owing to the thick muscle of the rectum and the absence of a mesentery only a slight degree of dilatation occurs, but the thinner walled and movable pelvic colon becomes enormously enlarged, both in diameter and length; the dilatation rarely extends beyond the junction of the pelvic colon with the iliac colon, as the latter is also devoid of a mesentery. The pelvic colon generally reaches the left dome of the diaphragm and may extend above the liver under the right dome. A secondary kink may occur at the pelvi-rectal junction, but the primary obstruction is always at the anal sphincter. Megacolon does not necessarily give rise to any symptoms, though constipation is generally present; toxæmia never occurs unless aperients are taken, but attacks of colic caused by over-distension with gas are common. Treatment by dilatation of the anal sphincter always gives more or less complete relief, and operative treatment is never indicated.

Drs. Starling, and Parkes Weber discussed this communication.

3. DR. HARRY CAMPBELL, in a contribution entitled *Some Aspects of British Diet*, gave an interesting account of the influence of agriculture, and of the effect on the teeth of modern diet.

4. DR. T. WARDROP GRIFFITH gave a communication on *Division of the Left Auricle into Two Compartments*. He showed a specimen of a heart from a child of six months old, who died with signs of congestive heart failure. The left auricle was divided into two chambers by a membranous septum; the upper chamber received the pulmonary veins; the lower chamber communicated with the left ventricle through a normal mitral valve aperture and with the cavity of the auricular appendix. A probe passed through a slightly patent foramen ovale showed that the right auricle was in communication with the lower of the two chambers of the left auricle. An imperfect fringe of vegetations was found on the margin of the aperture of communication between the upper and lower chambers, and this aperture was large enough to admit of the passage of a goose quill. He was inclined to regard the dividing septum as an exaggeration of, and allied to, the more imperfect septa or bands which are found in some cases to spread from the valvula foraminis ovalis ('retinacula'). In showing his first case of 'fibromuscular band passing across the left auricle' in 1896, Dr. Griffith had suggested to the Anatomical Society the possibility of the condition being due to an imperfect opening out of the communication between the left half of the primitive auricle and the left, or pulmonary sinus venosus, and this is supported by the present specimen.

5. DRS. F. R. FRASER, C. F. HARRIS, and J. A. DAUPHINEE (introduced), on *Calcium and Phosphorus Metabolism in Hyperparathyroidism*. Three cases of hyperparathyroidism were investigated, and the calcium and phosphorus metabolism estimated before and after removal of parathyroid tumours. The conclusions were:

(1) That the condition of hyperparathyroidism may at times diminish greatly in activity.

(2) That the phosphorus metabolism does not follow the calcium metabolism as might be expected.

(3) That phosphorus may be stored while calcium is being excreted in quantities in excess of the intake.

(4) That the most probable explanation is that phosphorus under these conditions is stored in the body in some form other than the calcium phosphates of bone.

Dr. Findlay did not believe that tetany is necessarily connected with the parathyroid.

Drs. D. Hunter and Ritchie discussed several points.

6. DR. C. G. IMRIE discussed *Some Observations on Post-encephalitic Bradypnoea*. A male, aged 31 years, had epidemic encephalitis in March 1924. He came under observation in September 1928, presenting clinical features of post-encephalitis parkinsonism and bradypnoea. The respiratory rate at complete rest varies from three to six per minute, the tidal air from 1,000 to 2,000 c.c. The diaphragm, examined roentgenologically, moves normally with inspiration, but the return to the expiratory position is very slow. The respiratory rate could be controlled volitionally; it quickened during work, speech, and to a slight degree in sleep. It was suggested that the condition was

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due to the persistence of inspiratory tonus, inhibition was not initiated until the lung tissue was distended to a greater degree than normal, and then the inhibition was incomplete giving rise to the prolongation of expiration.

The President stated that this is the only recorded case of bradypnoea following epidemic encephalitis.

7. DR. IAN G. W. HILL (introduced), under the title of *Carotovagal Reflexes*, gave an account of the reflexes arising from the carotid sinus and controlling heart-rate, blood-pressure, and respiration. The results of animal experiments were detailed, together with observations made upon the human subject during operations on the region of the carotid bifurcation, and the views of Hering regarding the reflex origin of bradycardia and 'vagal pressure' in man were substantiated.

2 p.m. to 3 p.m.

Demonstrations of Clinical Cases, Pathological Specimens, and Radiographs and Specimens illustrating Silicosis at the Royal Hospital.

3 p.m. Afternoon Session

1. DR. ROBERT COOPE gave a note on *Unresolved Pneumonia and Early Bronchiectasis*. He believed that both in children and adults, the important aetiological factor was a broncho-pneumonia which caused damage to the bronchioles, and invasion of the peribronchial, alveolar, and interstitial tissues. A broncho-pneumonia might result in complete recovery; in merely peribronchial thickening; an interstitial scarring which might extend also to the pleura; or in damage so severe as to bring about fibrotic dilatation of weakened bronchi, i.e. actual bronchiectasis.

2. DR. L. FINDLAY recorded the result of an *Analysis of 688 Examples of the Rheumatic Infection (Arthritis, Chorea, and Carditis) occurring during Childhood*. The conditions had occurred between the years 1911 and 1929, and the whole material was reviewed in 1930. With the exception of six of the examples, the ultimate fate or the present condition, if still alive, was known of them all. About 30 per cent. of the children had escaped implication of the heart. Of the cases in whom the heart was affected, one half, i.e. 30 per cent. of the total number died within ten years of the onset of the infection: a very large proportion, 37 per cent., died during the first year of the disease. The remaining 30 per cent. are still living, but more or less incapacitated. The ultimate fate of this group is problematical, but because the majority of rheumatic cardiac deaths occur during the age period, 35 to 45 years, it is presumed that for the most part they will die on reaching this age period of life. Since the age incidence of arteriosclerosis synchronizes in its onset with the period of increased rheumatic cardiac deaths, it is suggested that it is the onset of the degenerative cardiovascular changes which decides the fate of those examples of rheumatic heart disease who reach adult life.

3. DR. D. McALPINE made *Some Observations on Essential Arterial Hypertension*. He described several cases, three of them being in men under the age of 31, in which there was retinitis with papillitis associated with raised blood-pressure and little evidence of renal damage. The ophthalmoscopic picture was that described as 'renal' or 'albuminuric' retinitis. The term 'hypertensive' retinitis had recently been introduced in America to describe the retinal changes associated with essential hypertension, and his cases would seem to fall into this category. Manometric readings of the cerebrospinal fluid showed that as a rule the rise in intracranial tension was slight and was seldom great enough to account for the papilloedema. The aetiology of the retinitis in hypertension was discussed, and some evidence was brought forward in support of the theory of arteriole spasm.

4. DR. TERENCE EAST discussed *Calcification of Aortic Valves*. The calcification was most pronounced in the depth of the cusps. Usually there was fusion of the cusps. Sometimes calcified masses spread down into the septum, and in two instances had caused disturbances in conduction. There might also be calcification of the mitral valve, and in some cases the mitral valve alone was affected. The cause was obscure. Rheumatism is unlikely in view of the incidence on the aortic valves. Syphilis is not found. Certain points suggest an inflammatory cause—a very subacute endocarditis—but infarcts do not occur. Possibly the degenerative process causes the condition in some instances, and sclerosing endocarditis in others. Aortic stenosis, without a mitral lesion, is almost invariably due to this disease when it is met with in middle age or later.

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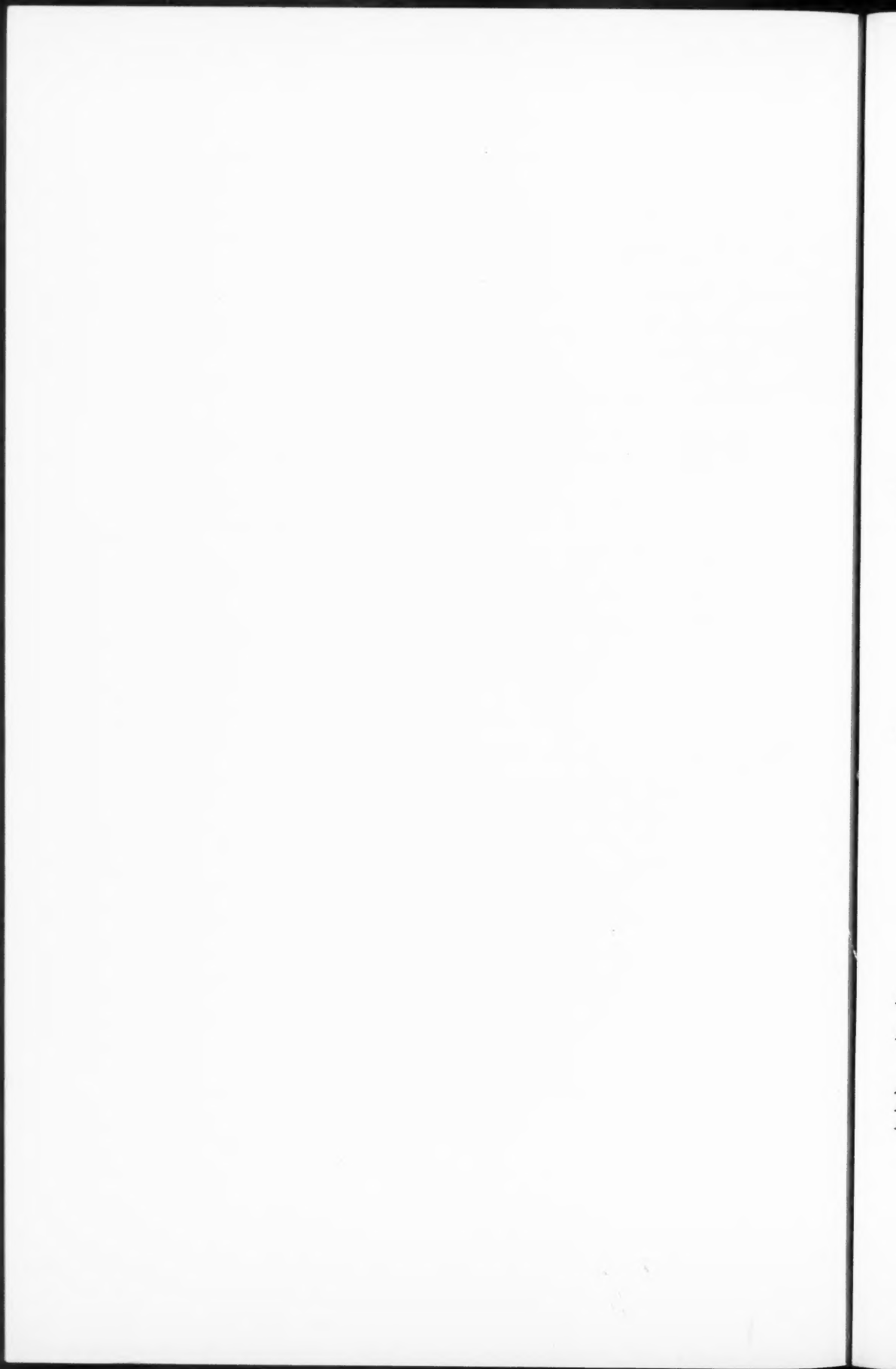
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